262266

Biological Psychology

An Introduction to Behavioral, Cognitive, and Clinical Neuroscience

FIFTH EDITION

S. Marc Breedlove
Michigan State University

Mark R. Rosenzweig
University of California, Berkeley

Neil V. Watson
Simon Fraser University

Maharishi Dayanand University Library
ROHTAK
262266

Sinauer Associates, Inc. • *Publishers* • *Sunderland, Massachusetts*

SHOUT
SHARE
IT

Biological Psychology: Scope and Outlook

A Brain on the Ceiling of the Sistine Chapel?

Between 1508 and 1512, Michelangelo (1475–1564) painted the Sistine Chapel in the Vatican. One panel of the ceiling, his masterpiece *The Creation of Adam* (shown on the opposite page), depicts God reaching out to bestow the gift of life upon humanity, through Adam. But the oddly shaped drapery behind God, and the arrangement of his attendants, has prompted speculation that Michelangelo was conveying a hidden message: God and attendants appear to be part of a human brain (Meshberger, 1990).

As illustrated here, only a little imagination is required to identify the broad outlines of a brain in Michelangelo's depiction of God (compare it with the midline section of a human brain in Figure 2.12*b*). During the Renaissance, when this fresco was created, the all-powerful Church forbade depiction of the dissected human body, considering it to be a desecration. But there is no doubt that Michelangelo engaged in extensive dissections of cadavers, gaining the detailed knowledge of human anatomy that informs his sculpture and paintings. It is highly likely that he knew perfectly well what a dissected human brain looks like. So, was Michelangelo making a subtle commentary about the origins of behavior? We probably will never know. But it is now clear that our uniquely human qualities—language, reason, emotion, and the rest—are products of the brain.

In this book we explore the many ways in which the structures and actions of the brain produce mind and behavior. But that is only half of our task. We are also interested in the ways in which behavior in turn modifies the structures and actions of the brain. One of the most important lessons we hope to convey is that interactions between brain and behavior are reciprocal. The brain controls behavior, and in turn, behavior alters the brain.

We hope to give an interesting account of the main ideas and research in biological psychology, which is of great popular as well as scientific interest. Because there are so many pieces to tie together, we try to introduce a given piece of information when it makes a difference to the understanding of a subject—especially when it forms part of a story. Most importantly, we seek to communicate our own interest and excitement about the mysteries of mind and body.

What Is Biological Psychology?

No treaty or trade union agreement has ever defined the boundaries of biological psychology. It is a field that includes many players who come from quite different backgrounds—psychologists, biologists, physiologists, engineers, neurologists, psychiatrists, and many others. It also shares concepts and research approaches with many other disciplines.

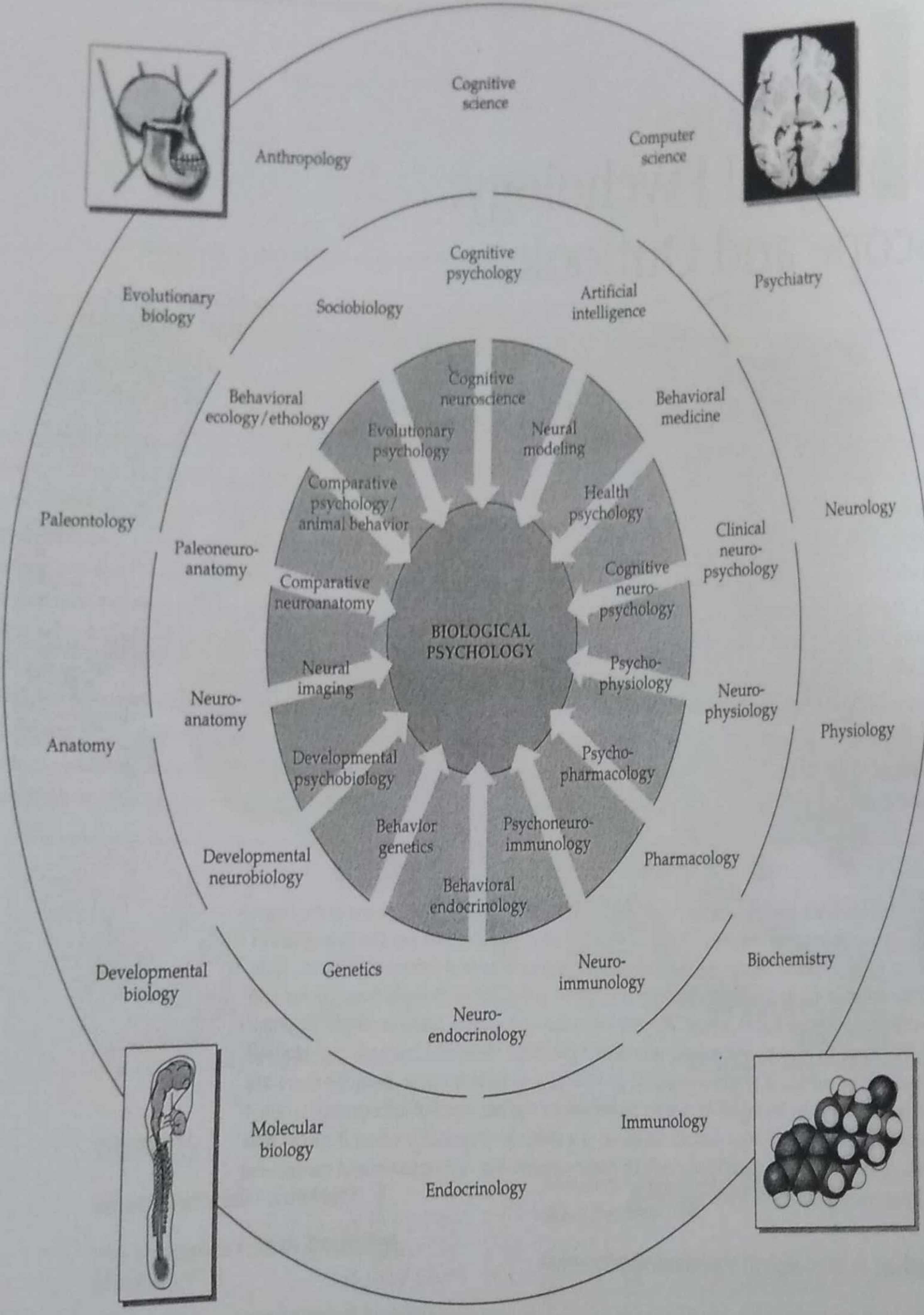
Biological psychology is the field that relates behavior to bodily processes, especially the workings of the brain. Because study of the brain is known as **neuroscience** (the root *neuro-* comes from the Greek word *neuron*, meaning "nerve" or "cord"), biological psychology is also known as **behavioral neuroscience**. Whichever name is used, the main goal of this field is to understand the biology underlying behavior and experience.

Like other sciences, biological psychology is also dedicated to improving the human condition. As Albert Einstein once said, concern for humanity and its fate must always form the chief interest of all scientific endeavors "in order that the creations of our minds

biological psychology The study of the biological bases of psychological processes and behavior.

neuroscience The study of the nervous system.

behavioral neuroscience The field of study concerned with the ways in which nervous system activity manifests in behavior.


Cognitive science
Anthropology
Computer science
Cognitive psychology
Evolutionary biology
Sociobiology
Artificial intelligence
Psychiatry
Cognitive neuroscience
Behavioral ecology/ethology
Evolutionary psychology
Neural modeling
Behavioral medicine
Comparative psychology/animal behavior
Health psychology
Paleontology
Neurology
Paleoneuro-anatomy
Clinical neuro-psychology
Comparative neuroanatomy
Cognitive neuro-psychology
BIOLOGICAL PSYCHOLOGY
Neural imaging
Psycho-physiology
Neuro-anatomy
Neuro-physiology
Anatomy
Physiology
Developmental psychobiology
Psycho-pharmacology
Behavior genetics
Psychoneuro-immunology
Developmental neurobiology
Pharmacology
Behavioral endocrinology
Developmental biology
Genetics
Neuro-immunology
Biochemistry
Neuro-endocrinology
Molecular biology
Immunology
Endocrinology

1.1 How Biological Psychology Relates to Other Fields of Study In this graphical representation of the relationships among biological psychology and other scientific disciplines, fields toward the center of the map are closest to biological psychology in their history, outlook, aims, and/or methods.

shall be a blessing and not a curse.” **Figure 1.1** maps the relations of biological psychology to other disciplines. Clearly the biological psychology umbrella is very wide.

Five Viewpoints Explore the Biology of Behavior

In our pursuit to understand the biological bases of behavior, we use several different perspectives. Because each one yields information that complements the others, the combination of perspectives is especially powerful. The five major perspectives are

TABLE 1.1 Five Research Perspectives Applied to Three Kinds of Behavior

Research perspective	Kind of behavior: Sexual behavior	Learning and memory	Language and communication
DESCRIPTION			
Structural	What are the main patterns of reproductive behavior and sex differences in behavior?	In what main ways does behavior change as a consequence of experience—for example, conditioning?	How are the sounds of speech patterned?
Functional	How do specialized patterns of behavior contribute to mating and to care of young?	How do certain behaviors lead to rewards or avoidance of punishment?	What behavior is involved in making statements or asking questions?
EVOLUTION	How does mating depend on hormones in different species?	How do different species compare in kinds and speed of learning?	How did the human speech apparatus evolve?
DEVELOPMENT	How do reproductive and secondary sex characteristics develop over the life span?	How do learning and memory change over the life span?	How do children learn to speak?
MECHANISM	What neural circuits and hormones are involved in reproductive behavior?	What anatomical and chemical changes in the brain hold memories?	What brain regions are particularly involved in language?
APPLICATIONS	Low doses of testosterone restore libido in some postmenopausal women.	Gene therapy and behavioral therapy improve memory in some senile patients.	Speech therapy, in conjunction with amphetamine treatment, speeds language recovery following stroke.

1. *Describing* behavior
2. Studying the *evolution* of behavior
3. Observing the *development* of behavior and its biological characteristics over the life span
4. Studying the biological *mechanisms* of behavior
5. Studying *applications* of biological psychology—for example, its applications to dysfunctions of human behavior

These perspectives are discussed in the sections that follow, and **Table 1.1** shows how each perspective can be applied to three kinds of behavior.

①

Behavior can be described according to different criteria

Until we describe what we want to study, we cannot accomplish much. Depending on the goals of our investigation, we may describe behavior in terms of detailed acts or processes, or in terms of results or functions. An analytical description of arm movements might record the successive positions of the limb or the contraction of different muscles. A functional behavioral description, on the other hand, would state whether the limb was being used in walking, running, hopping, swimming, or shooting dice. To be useful for scientific study, a description must be precise and reveal the essential features of the behavior, using accurately defined terms and units.

②

We compare species to learn how the brain and behavior have evolved

Darwin's theory of evolution through natural selection is central to all modern biology and psychology. From this perspective emerge two rather different emphases: (1) the *continuity* of behavior and biological processes among species because of common ancestry and (2) the species-specific *differences* in behavior and biology that have evolved as adaptations to different environments. At some points in this book we will concentrate on continuity—that is, features of behavior and its biological mechanisms that are common to many species. At other points, we will look at species-specific behaviors.

Darwin theo

differences btw species

co btw

Nature is conservative. Once particular features of the body or behavior have evolved, they may be maintained for millions of years and may be seen in animals that otherwise appear very different. For example, the electrical messages used by nerve cells (see Chapter 3) are essentially the same in a jellyfish, a cockroach, and a human being. Some of the chemical compounds that transmit messages through the bloodstream (hormones) are also the same in diverse animals. Species share such **conserved** characteristics because the features first arose in a shared ancestor (**Box 1.1**). But mere similarity of a feature between species does not guarantee that the feature came from a common ancestral species. Similar solutions to a problem may have evolved independently in different classes of animals.

③

The body and behavior develop over the life span

Ontogeny is the process by which an individual changes in the course of its lifetime—that is, grows up and grows old. Observing the way in which a particular behavior changes during ontogeny may give us clues to its functions and mechanisms. For example, we know that learning ability in monkeys increases over several years of development. Therefore, we can speculate that prolonged maturation of brain circuits is required for complex learning tasks. In rodents the ability to form long-term memories lags somewhat behind the maturation of learning ability. So, young rodents learn well but forget more quickly than older ones, suggesting that learning and memory involve different processes. Studying the development of reproductive capacity and of differences in behavior between the sexes, along with changes in body structures and processes, enables us to throw light on body mechanisms of sex behaviors.

④

Biological mechanisms underlie all behavior

The history of a species tells us the evolutionary determinants of its behavior; the history of an individual tells us the developmental determinants. To learn about the mechanisms of an individual's behavior, we study how his or her present body works. To understand the underlying mechanisms of behavior, we must regard the organism (with all due respect) as a "machine," made up of billions of nerve cells, or **neurons** (the Greek word for "nerve" or "cord"). We must ask, How is this thing constructed to be able to do all that?

Our major aim in biological psychology is to examine body mechanisms that make particular behaviors possible. In the case of learning and memory, for example, we would like to know the sequence of electrical and biochemical processes that occur when we learn something and retrieve it from memory. What parts of the nervous system are involved in that process? In the case of reproductive behavior, we would like to know how the body grows to produce the capacity for sexual behavior. We also want to understand the neuronal and hormonal processes that underlie reproductive behavior.

⑤

Research can be applied to human problems

A major goal of biological psychology is to use research findings to improve the health and well-being of humans and other animals. Numerous human diseases involve malfunctioning of the brain. Many of these are already being alleviated as a result of research in the neurosciences, and the prospects for continuing advances are good. Attempts to apply knowledge also benefit basic research. For example, the study of memory disorders in humans has pushed investigators to extend our knowledge of the brain regions involved in different kinds of memory (see Chapter 17).

Three Approaches Relate Brain and Behavior

Biological psychologists use three approaches to understand the relationship between brain and behavior: somatic intervention, behavioral intervention, and correlation. In the most common approach, **somatic intervention** (**Figure 1.2*a***), we alter a structure or function of the brain or body to see how this alteration changes behavior. Here, somatic intervention is the **independent variable**, and the behavioral effect is the **dependent vari-**

conserved In the context of evolution, referring to a trait that is passed on from a common ancestor to two or more descendant species.

✓ **ontogeny** The process by which an individual changes in the course of its lifetime—that is, grows up and grows old.

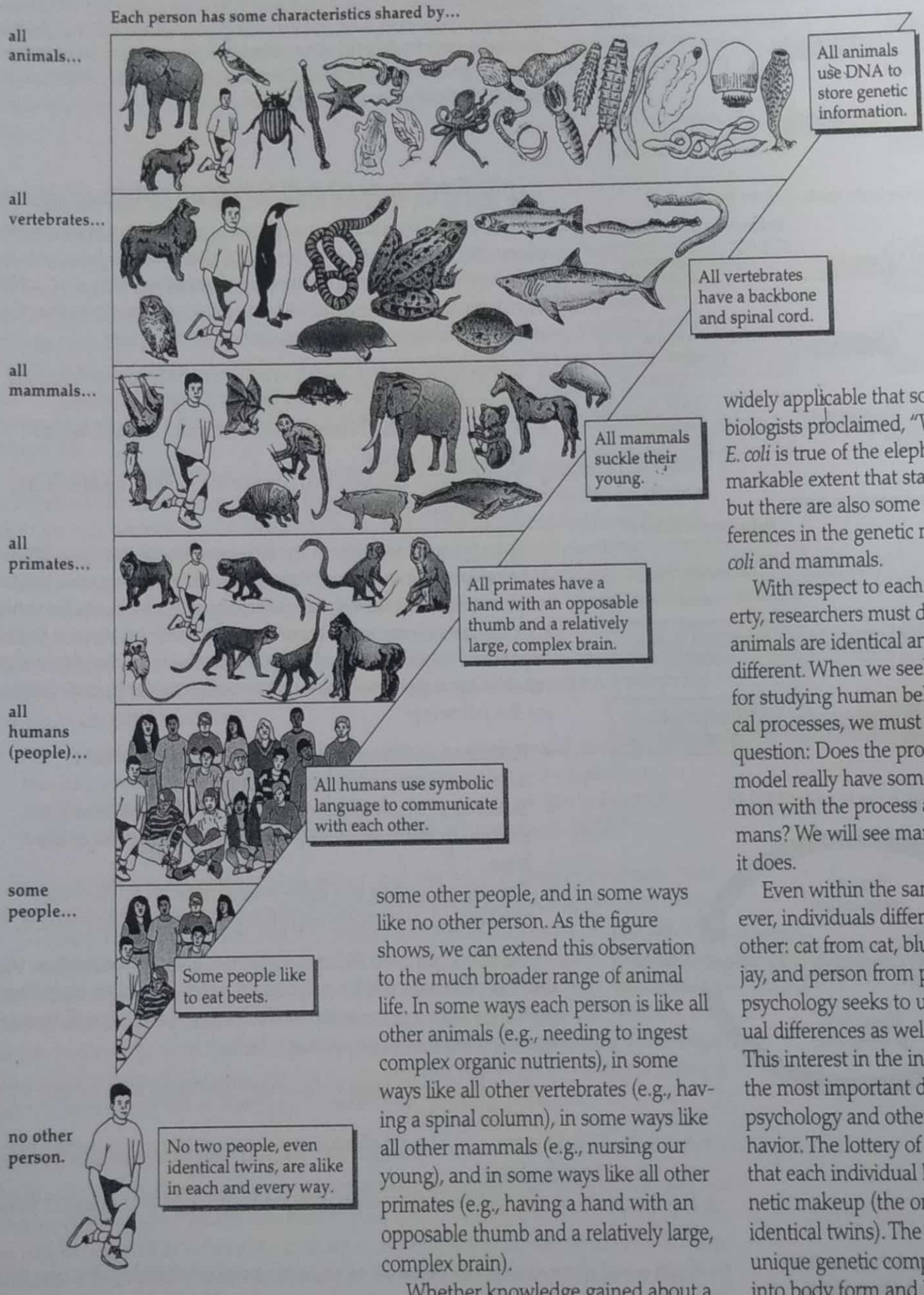
neuron Also called *nerve cell*. The basic unit of the nervous system.

somatic intervention An approach to finding relations between body variables and behavioral variables that involves manipulating body structure or function and looking for resultant changes in behavior.

independent variable The factor that is manipulated by an experimenter.

dependent variable The factor that an experimenter measures to monitor a change in response to changes in an independent variable.

BOX 1.1 We Are All Alike, and We Are All Different


Each person has some characteristics shared by...
all animals...
All animals use DNA to store genetic information.
all vertebrates...
All vertebrates have a backbone and spinal cord.
all mammals...
All mammals suckle their young.
all primates...
All primates have a hand with an opposable thumb and a relatively large, complex brain.
all humans (people)...
All humans use symbolic language to communicate with each other.
some people...
Some people like to eat beets.
no other person.
No two people, even identical twins, are alike in each and every way.

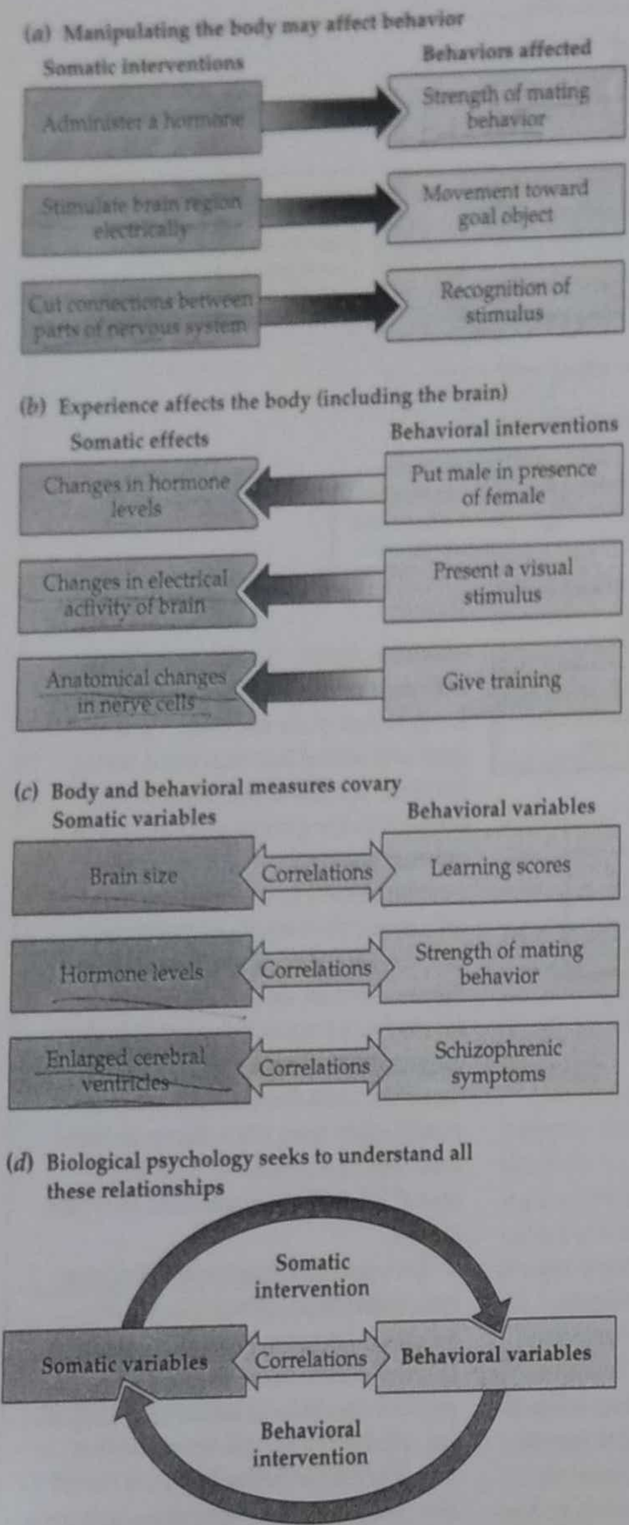
How do similarities and differences among people and animals fit into biological psychology? The anthropologist Clyde Kluckhohn (1949) observed that each person is in some ways like all other people, in some ways like some other people, and in some ways like no other person. As the figure shows, we can extend this observation to the much broader range of animal life. In some ways each person is like all other animals (e.g., needing to ingest complex organic nutrients), in some ways like all other vertebrates (e.g., having a spinal column), in some ways like all other mammals (e.g., nursing our young), and in some ways like all other primates (e.g., having a hand with an opposable thumb and a relatively large, complex brain).

Whether knowledge gained about a process in another species applies to humans depends on whether we are like that species in regard to that process. The fundamental research on the mechanisms of inheritance in the bacterium *Escherichia coli* proved so widely applicable that some molecular biologists proclaimed, "What is true of *E. coli* is true of the elephant." To a remarkable extent that statement is true, but there are also some important differences in the genetic mechanisms of *E. coli* and mammals.

With respect to each biological property, researchers must determine how animals are identical and how they are different. When we seek animal models for studying human behavior or biological processes, we must ask the following question: Does the proposed animal model really have some things in common with the process at work in humans? We will see many cases in which it does.

Even within the same species, however, individuals differ from one another: cat from cat, blue jay from blue jay, and person from person. Biological psychology seeks to understand individual differences as well as similarities. This interest in the individual is one of the most important differences between psychology and other approaches to behavior. The lottery of heredity ensures that each individual has a unique genetic makeup (the only exception being identical twins). The way the individual's unique genetic composition is translated into body form and behavioral capacities is part of our story. Furthermore, each individual has a unique set of personal experiences. Therefore, the way in which each person is able to process information and store the memories of these experiences is another part of our story.

9839065574


(a) Manipulating the body may affect behavior
Somatic interventions
Behaviors affected
Administer a hormone
Strength of mating behavior
Stimulate brain region electrically
Movement toward goal object
Cut connections between parts of nervous system
Recognition of stimulus
(b) Experience affects the body (including the brain)
Somatic effects
Behavioral interventions
Changes in hormone levels
Put male in presence of female
Changes in electrical activity of brain
Present a visual stimulus
Anatomical changes in nerve cells
Give training
(c) Body and behavioral measures covary
Somatic variables
Behavioral variables
Brain size
Correlations
Learning scores
Hormone levels
Correlations
Strength of mating behavior
Enlarged cerebral ventricles
Correlations
Schizophrenic symptoms
(d) Biological psychology seeks to understand all these relationships
Somatic intervention
Somatic variables
Correlations
Behavioral variables
Behavioral intervention

1.2 Three Main Approaches to Studying the Neuroscience of Behavior (*a*) In somatic intervention, investigators change the body structure or chemistry of an animal in some way and observe and measure any resulting behavioral effects. (*b*) Conversely, in behavioral intervention, researchers change an animal's behavior or its environment and try to ascertain whether the change results in physiological or anatomical changes. (*c*) Measurements of both kinds of variables allow researchers to arrive at correlations between somatic changes and behavioral changes. (*d*) Each approach enriches and informs the others.

able; that is, the resulting behavior depends on how the brain has been altered. For example, in response to mild electrical stimulation of one part of her brain, not only did one patient laugh, but she found whatever she happened to be looking at amusing (Fried et al., 1998).

In later chapters we describe many kinds of somatic intervention with both humans and other animals—for example:

- A hormone is administered to some animals but not to others; various behaviors of the two groups are later compared.
- A part of the brain is stimulated electrically, and behavioral effects are observed.
- A connection between two parts of the nervous system is cut, and changes in behavior are measured.

The approach opposite to somatic intervention is psychological, or **behavioral, intervention** (**Figure 1.2*b***). In this approach, the scientist intervenes in the behavior of an organism and looks for resulting changes in body structure or function. Here behavior is the independent variable, and change in the body is the dependent variable. Among the examples that we will consider in later chapters are the following:

- Putting two adults of opposite sex together may lead to increased secretion of certain hormones.
- Exposing a person or animal to a visual stimulus provokes changes in electrical activity and blood flow in parts of the brain.
- Training of animals in a maze is accompanied by electrical, biochemical, and anatomical changes in parts of their brains.

The third approach to brain–behavior relations, **correlation** (**Figure 1.2*c***), consists of finding the extent to which a given body measure varies with a given behavioral measure. Later we will examine the following questions, among others:

- Are people with large brains more intelligent than people with smaller brains?
- Are individual differences in sexual behavior correlated with levels of certain hormones in the individuals?
- Is the severity of schizophrenia correlated with the magnitude of changes in brain structure?

Such correlations should not be taken as proof of causal relationship. For one thing, even if a causal relation exists, the correlation does not reveal its direction—that is, which variable is independent and which is dependent. For another, two factors might be correlated only because a third, unknown factor affects the two factors measured. What a correlation does indicate is that the two variables are linked in some way—directly or indirectly. Such a correlation often stimulates investigators to formulate hypotheses and to test them by somatic or behavioral intervention.

behavioral intervention An approach to finding relations between body variables and behavioral variables that involves intervening in the behavior of an organism and looking for resultant changes in body structure or function.

correlation The covariation of two measures.

Combining these three approaches yields the circle diagram of **Figure 1.2*d***. This diagram incorporates the basic approaches to studying relationships between bodily processes and behavior. It also emphasizes the theme that the relations between brain and body are reciprocal: each affects the other in an ongoing cycle of bodily and behavioral interactions. We will see examples of this reciprocal relationship throughout the book.

Neural Plasticity: Behavior Can Change the Brain

The idea that there is a reciprocal relationship between brain and behavior has embedded within it a concept that is, for most people, startling. When we say that behavior and experience affect the brain, we mean that they, literally, physically alter the brain. The brain of a child growing up in a French-speaking household assembles itself into a configuration that is different from the brain of a child who hears only English. That's why the first child, as an adult, understands French effortlessly while the second does not. In this case we cannot tell you what the structural differences are exactly, but we do know one part of the brain that is being altered by these different experiences (see Chapter 19).

Numerous examples, almost all in the animal literature, show that experience has been demonstrated to affect the number or size of neurons, or the number or size of connections between neurons. This ability of the brain, both in development and in adulthood, to be changed by the environment and by experience, is called **neural plasticity**.

Today when we hear the word *plastic*, we think of the class of materials found in so many modern products. But originally *plastic* meant "flexible, malleable" (from the Greek *plassein*, "to mold or form"), and the modern materials were named *plastics* because they can be molded into nearly any shape. In 1890, William James (1842–1910) described plasticity as the possession of a structure weak enough to yield to an influence but strong enough not to yield all at once:

> Nervous tissue seems endowed with a very extraordinary degree of plasticity of this sort; so that we may without hesitation lay down as our first proposition the following, that the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed. (p. 110)

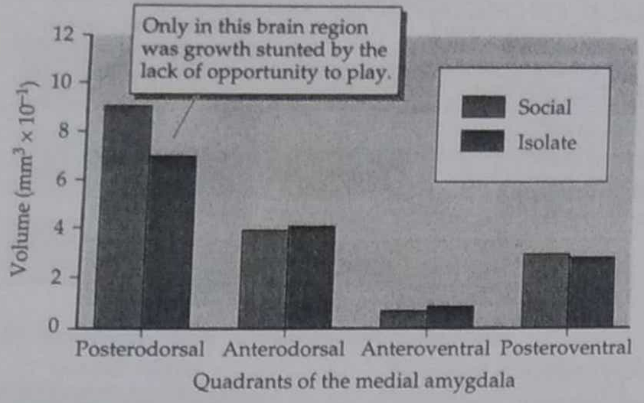
In the ensuing years, research has shown that the brain is even more plastic than James suspected. For example, parts of neurons known as dendritic spines (see Chapter 2) appear to be in constant motion, changing shape in the course of seconds (Fischer et al., 1998). We will see many examples in which experience alters the structure and/or function of the brain. In Chapter 5, hearing a baby cry will cause the mother's brain to secrete a hormone; in Chapter 7, visual experience in kittens will direct the formation of connections in the brain; in Chapter 12, a mother rat's grooming of her pups will affect the survival of spinal cord neurons; and in Chapter 18, a sea slug learning a task will strengthen the connections between two particular neurons.

Biological and social psychology are related

The plasticity of the human brain has a remarkable consequence: other individuals can have an effect on the physical structure of your brain! Indeed, the whole point of coming to a lecture hall is to have the instructor use words and figures to alter your brain, so that you can retrieve that information in the future (in other words, she is teaching you something). Many of these alterations in your brain last only until you take an exam, but every once in a while the instructor may tell you something that you'll remember for the rest of your life. Most aspects of our social behavior are learned—from the language we speak to the clothes we wear and the kinds of food we eat—so our examination of the mechanisms of learning and memory (see Chapters 17 and 18) is important for understanding social behavior.

For an example from an animal model, consider the fact that rats spend a lot of time investigating the smells around them, including those coming from other rats. Cooke et al. (2000) took young rats, just weaned from their mother, and either raised each male

neural plasticity Also called *ne*
plasticity. The ability of the nerv
to change in response to experie
environment.



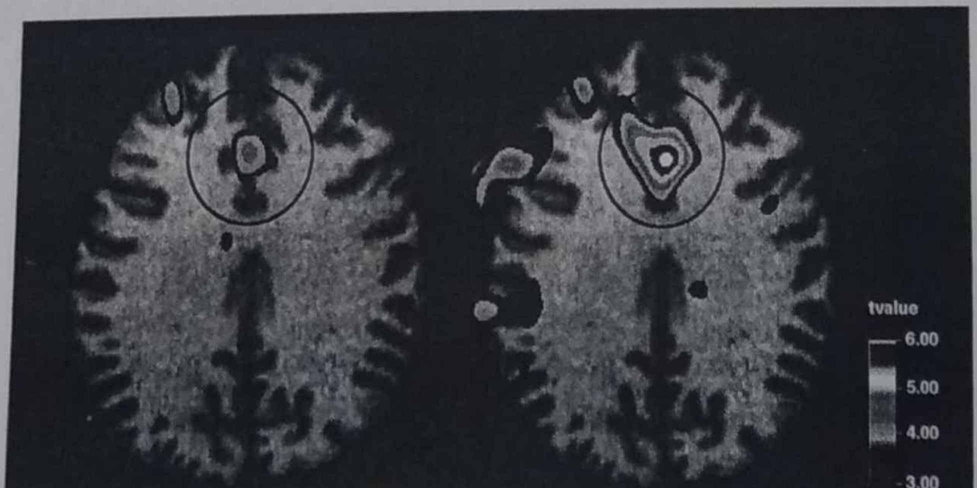
1.3 The Role of Play in Brain Development A brain region involved in processing odors (the posterodorsal portion of the medial amygdala) was smaller in male rats housed individually compared to males housed together and allowed to play. Other nearby regions were identical in the two groups. (After Cooke et al., 2000.)

in a cage alone, or raised them with other males to play with. Examination of these animals as adults found only one brain difference between the groups: a region of the brain known to process odors was smaller in the isolated males than in the males raised with playmates (**Figure 1.3**). Was it the lack of play (Gordon et al., 2003), the lack of odors to investigate, or the stress of isolation that made the region smaller? Whatever the mechanism, social experience affects this brain structure. In Chapter 18 we'll see that social experience also enhances the effects of environmental enrichment on brain growth.

Here's an example of how social influences can affect the human brain. When people were asked to put a hand into moderately hot water (47°C), part of the brain became active, presumably because of the discomfort involved (Rainville et al., 1997). But subjects who were led to believe the water would be *very* hot had a more activated brain than subjects who were led to believe the discomfort would be minimal (**Figure 1.4**), even though the water was the same temperature for all subjects. The socially induced psychological expectation affected the magnitude of the brain response, even though the physical stimulus was exactly the same. (By the way, the people with the more activated brains also reported that their hands hurt more.)

In most cases, biological and social factors continuously interact and affect each other in an ongoing series of events as behavior unfolds. For example, the level of the hormone testosterone in a man's circulation affects his dominance behavior and aggression (see Chapter 15). The dominance may be exhibited in a great variety of social settings, ranging from playing chess to physical aggression. In humans and other primates, the level of testosterone correlates positively with the degree of dominance and with the amount of aggression exhibited. Winning a contest, whether a game of chess or a boxing match, raises the level of testosterone; losing a contest lowers the levels. Thus, at any moment the level of testosterone is determined, in part, by recent dominant–submissive social experience, and the level of testosterone determines, in part, the degree of dominance and aggression in the future. Of course, social and cultural factors also help determine the frequency of aggression; cross-cultural differences in rates of aggression exist that cannot be correlated with hormone levels, and ways of expressing aggression and dominance are influenced by sociocultural factors.

Perhaps nothing distinguishes biological psychology from other neurosciences more clearly than the fascination with neural plasticity and the role of experience. Biological psychologists have a pervasive interest in how experience physically alters the brain and therefore affects future behavior. We will touch on this theme in almost every chapter of this book and review some of these examples again in the afterword.



1.4 Pictures of Pain Subjects told to expect only mild discomfort from putting a hand into 47°C water (*left*) showed less activation in a particular brain region (the anterior cingulate cortex) than subjects expecting more discomfort (*right*) from water of the very same temperature. Areas of high activation are indicated by orange, red, and white. (From Rainville et al., 1997; courtesy of Pierre Rainville.)

Biological Psychologists Use Several Levels of Analysis

Finding explanations for behavior often requires several levels of biological analysis. The units of each level of analysis are simpler in structure and organization than those of the level above. **Figure 1.5** shows how the **levels of analysis** range from social interactions to the brain, continuing to successively less complex units until we arrive at single nerve cells and their even simpler, molecular constituents.

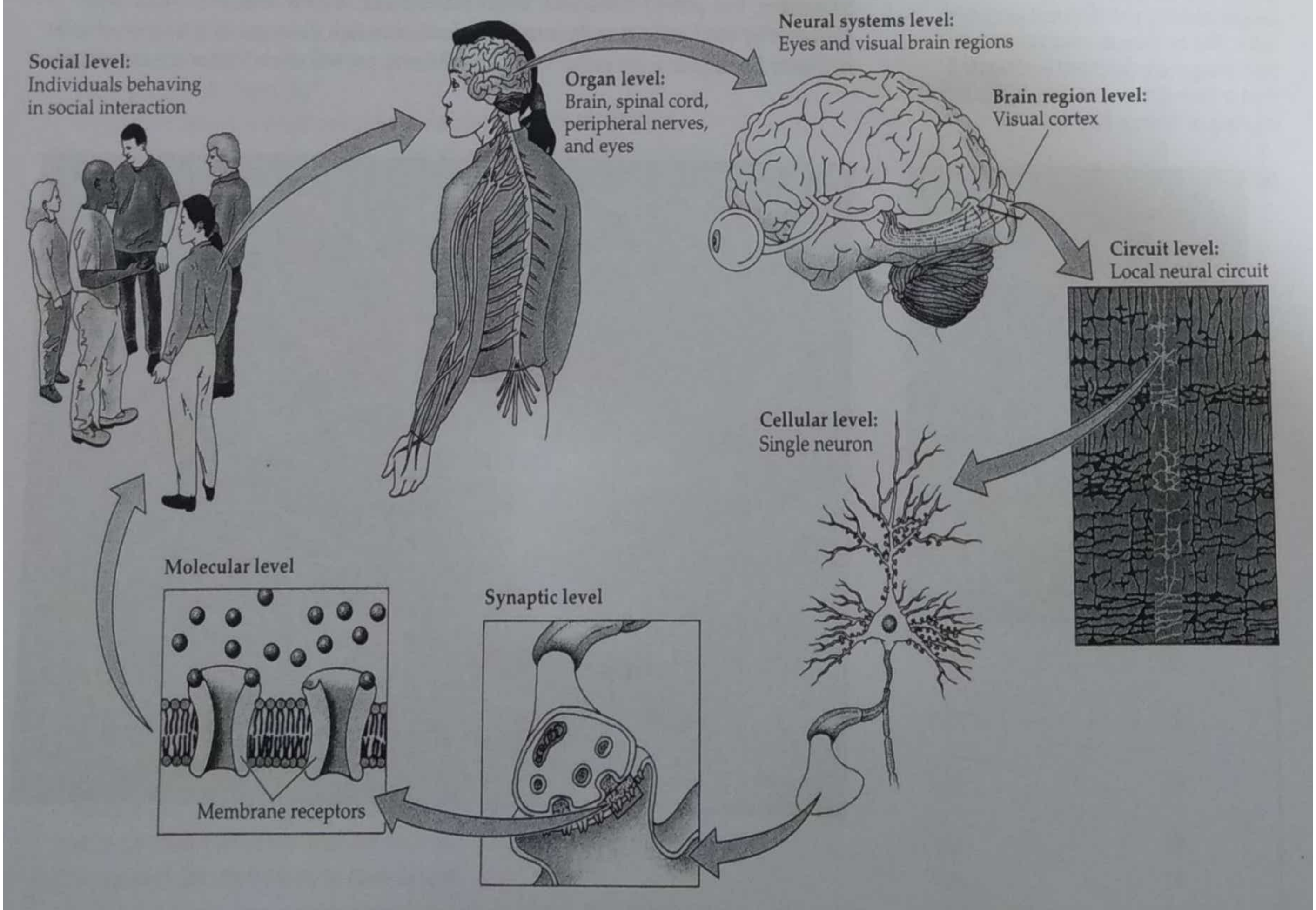
Scientific explanations usually involve analysis on a simpler or more basic level of organization than that of the structure or function to be explained. This approach is known as **reductionism**. In principle it is possible to reduce each explanatory series down to the molecular or atomic level, though for practical reasons this extent of reductionism is rare. For example, most chemists deal with large, complex molecules and the laws that govern them; seldom do they seek explanations in terms of atoms.

Naturally, in all fields different problems are carried to different levels of analysis, and fruitful work is often being done simultaneously by different workers at several levels. Thus, in their research on visual perception, cognitive psychologists advance analytical descriptions of behavior. They try to determine how the eyes move while looking at a visual pattern, or how the contrast among parts of the pattern determines its visibility. Meanwhile, other biological psychologists study the differences in visual endowments among species and try to determine the adaptive significance of these differences. For example, how is the presence (or absence) of color vision related to the life of a species? At the same time, other investigators trace out brain structures and networks involved in different kinds of visual discrimination. Still other scientists try to ascertain the electrical and chemical events that occur in the brain during vision.

levels of analysis The scope of experimental approaches. A scientist may try to understand behavior by monitoring molecules, nerve cells, brain regions or social environments, or some combination of these levels of analysis.

reductionism The scientific strategy of breaking a system down into increasingly smaller parts in order to understand it.

1.5 Levels of Analysis in Biological Psychology The scope of biological psychology ranges from the level of the individual interacting with others, to the level of the molecule. Depending on the question at hand, investigators use different techniques to focus on these many levels, but always with an eye toward how their findings apply to behavior.


Social level:
Individuals behaving in social interaction
Organ level:
Brain, spinal cord, peripheral nerves, and eyes
Neural systems level:
Eyes and visual brain regions
Brain region level:
Visual cortex
Circuit level:
Local neural circuit
Cellular level:
Single neuron
Synaptic level
Molecular level
Membrane receptors

A Preview of the Book: Fables and Facts about the Brain

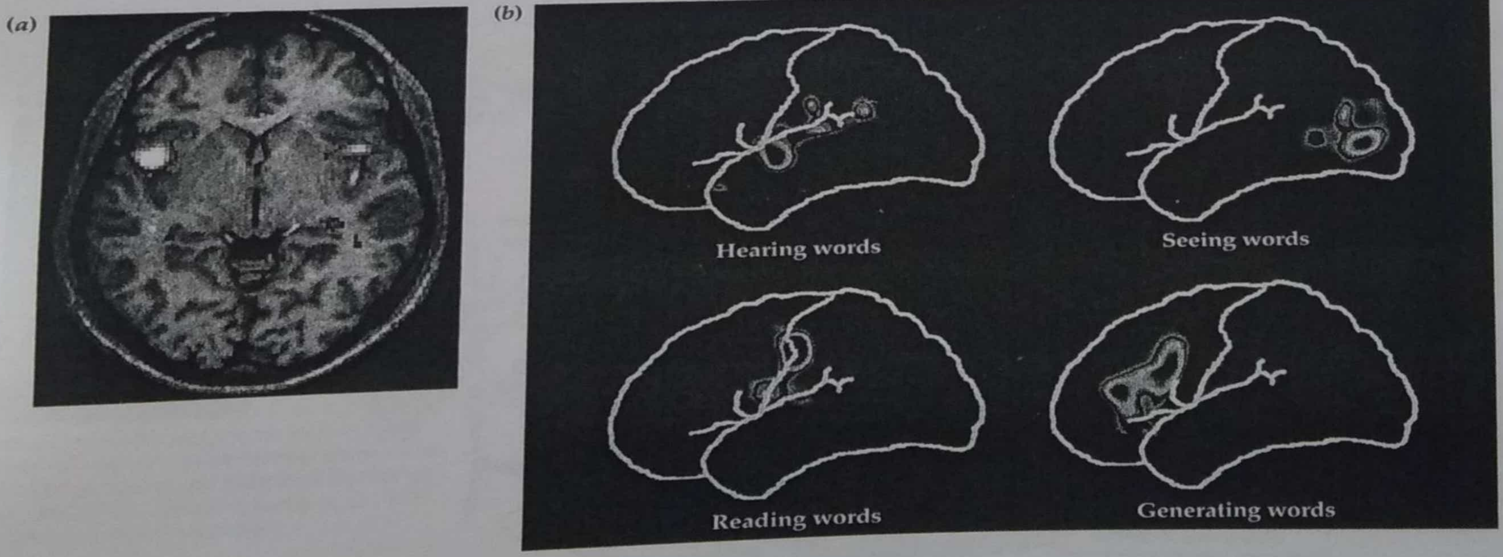
Here are some examples of research topics considered in this book:

- How does the brain grow, maintain, and repair itself over the life span, and how are these capacities related to the growth and development of the mind and behavior from the womb to the tomb?
- How does the nervous system capture, process, and represent information about the environment? For example, sometimes brain damage causes a person to lose the ability to identify other people's faces; what does that tell us about how the brain recognizes faces?
- How does sexual orientation develop? Some brain regions are different in heterosexual versus homosexual men; what do those differences tell us about the development of human sexual orientation?
- What brain sites and activities underlie feelings and emotional expression? Are particular parts of the brain active in romantic love, for example (**Figure 1.6*a***)?
- Some people suffer damage to the brain and afterward seem alarmingly unconcerned about dangerous situations and unable to judge the emotions of other people; what parts of the brain are damaged to cause such changes?
- How does the brain manage to change during learning, and how are memories retrieved?
- Why are different brain regions active during different language tasks (**Figure 1.6*b***)?

The relationship between the brain and behavior is, on the one hand, very mysterious because it is difficult to understand how a physical device, the brain, could be responsible for our subjective experiences of fear, love, and awe. Yet despite this mystery, we all use our brains every day. Perhaps it is the "everyday miracle" aspect of the topic that has generated so much folk wisdom about the brain.

Sometimes these popular ideas about the brain are in line with our current knowledge, but in many cases we know they are false. For example, the notion that we normally use only a tenth (or a third, or a half, or some other fraction) of our brain is commonplace, but patent nonsense. Brain scans make it clear that the entire brain is activated by even fairly mundane tasks. Indeed, although the areas of activation shown in Figure 1.6 appear to be rather small and discrete, we will show in Box 2.3 that exper-

1.6 "Tell Me Where Is Fancy Bred?" (*a*) The parts of the brain highlighted here become especially active when a person thinks about his or her romantic partner. (*b*) Different brain regions are activated when people perform four different language tasks. The techniques used to generate such images are described in Chapter 2. (Part *a* from Bartels and Zeki, 2000; part *b* courtesy of Marcus Raichle.)



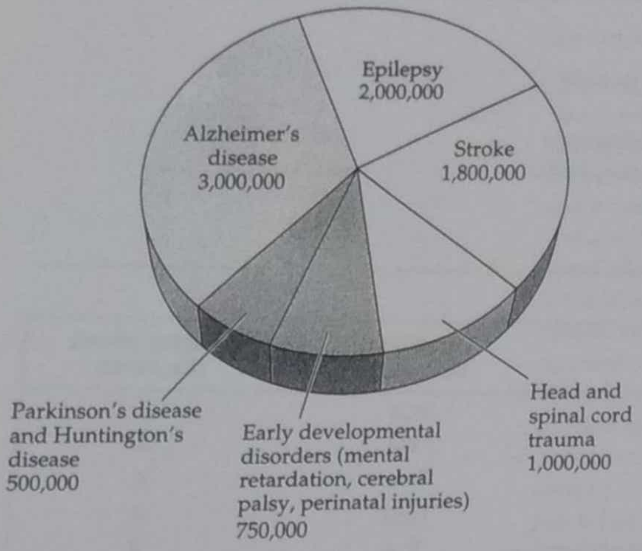
imenters must work very hard to create images that separate activation related to a particular task from the background of widespread, ongoing brain activity.

In fact, it's fairly easy to reel off a host of commonly held beliefs about the relationships between the brain and behavior. **Table 1.2** presents a list of such beliefs that you may have heard, interspersed with some claims that are true but may sound improbable.

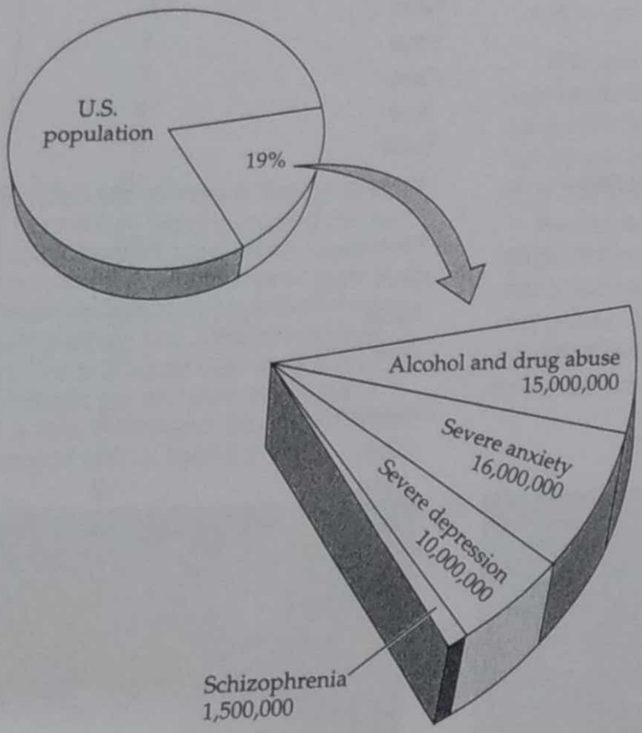
TABLE 1.2 Facts or Fables of Biological Psychology?

Statement	True/False/ Uncertain	Chapter where discussed
Some human nerve cells are more than 3 feet long.	True	2
Nerve impulses travel at the speed of light.	False	3
More people die each year from the use of legal drugs than illegal drugs.	True	4
Only humans ingest mind-altering substances.	False	4
Our bodies make chemicals that are similar in structure to heroin and marijuana and act on the same sites in the brain.	True	4
Testosterone is made only by males, and estrogen is made only by females.	False	5
Only humans have created cultures.	False	6
Once our brains are developed, we can never grow new nerve cells.	False	7
Some people are incapable of feeling pain.	True	8
Different parts of the tongue are specialized to recognize certain tastes.	False	9
The brightness and color of the objects we see are creations of our perceptual systems, not properties of the objects themselves.	True	10
Dogs are color-blind.	False	10
Each side of the brain controls the muscles on the opposite side of the body.	True	11
There are no anatomical differences between men's and women's brains.	False	12
In some animal species every individual is female. In some other species, individuals can change sex during their lifetimes.	True	12
Some people are "born gay."	Uncertain	12
Most of our energy is expended just maintaining our body temperature.	True	13
We can lose weight permanently by surgically removing fat from our bodies.	False	13
The peaks in cases of depression and suicide occur around Christmas holidays.	False	14
During sleep the brain is relatively inactive.	Not always	14
Sleepwalkers are acting out dreams.	False	14
Prolonged sleep deprivation will make you temporarily crazy.	False	14
Some animals can have half their brain asleep and the other half awake.	True	14
The left side of the face is more emotionally expressive than the right side.	True	15
Prolonged stress can cause heart disease.	True	15
All cultural groups recognize the same facial expressions for various emotions.	Uncertain	15
It is possible to determine scientifically whether someone is lying.	False (for now)	15
Scientists are not sure why antidepressant drugs work.	True	16
People in northern countries are more susceptible to seasonal depression.	Uncertain	16
Some people are incapable of producing any new memories.	True	17
We never really forget anything that we have experienced.	Uncertain	17
Each memory is stored in its own brain cells.	False (probably)	18
We can change the structure of an animal's brain by raising it in a more stimulating environment.	True	18
People are "right-brained" or "left-brained": dominance of the left or right hemisphere of the brain accounts for major differences in people's cognitive styles or personalities.	False	19
Some brain disorders cause people to lose the ability to recognize faces. In other disorders, patients are unable to name only certain kinds of animals or certain kinds of food.	True	19
A child can have half of the brain removed and still develop normal intelligence.	True	19
Chimpanzees can use symbols to communicate.	True	19

(a) Prevalence of neurological disorders



(b) Incidence of psychiatric disorders



1.7 The Toll of Brain Disorders As these pie charts show, neurological (a) and psychiatric (b) disorders are quite common n the United States. As brain research pro- resses, the distinction between psychiatric nd neurological disorders begins to seem rtificial or arbitrary.

Neuroscience Contributes to Our Understanding of Psychiatric Disorders

One of the great promises of biological psychology is that it can help us understand brain disorders and devise treatment strategies. Like any other complex mechanism, the brain is subject to a variety of malfunctions and breakdowns. People afflicted by disorders of the brain are not an exotic few. At least one person in five around the world currently suffers from neurological and/or psychiatric disorders that vary in severity from complete disability to significant changes in quality of life.

Figure 1.7*a* shows the estimated numbers of U.S. residents afflicted by some of the main neurological disorders. **Figure 1.7*b*** gives estimates of the numbers of U.S. adults who suffer from certain major psychiatric disorders. The percentage of U.S. adults suffering from mental illness may be increasing (Torrey, 2002).

The toll of these disorders is enormous, in terms of both individual suffering and social costs (Demyttenaere et al., 2004). The National Advisory Mental Health Council estimated that direct and indirect costs of behavioral and brain disorders amount to $400 billion a year in the United States. For example, the cost for treatment of dementia (severely disordered thinking) exceeds the costs of treating cancer and heart disease combined. The World Health Organization (2004) estimates that over 15% of all disease burden, in terms of lost productivity, is due to mental disorders. The high cost in suffering and expense has compelled researchers to try to understand the mechanisms involved in these disorders and to try to alleviate or even prevent them.

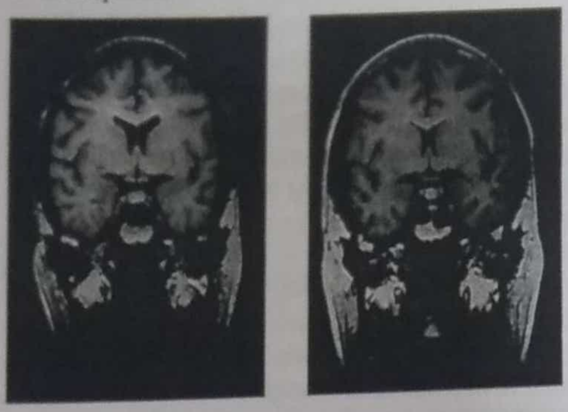
In this quest, the distinction between clinical and laboratory approaches begins to fade away. For example, when clinicians encounter a pair of twins, one of whom has schizophrenia while the other seems healthy, the discovery of structural differences in their brains (**Figure 1.8**) immediately raises questions for laboratory scientists. Did the structural differences arise before the symptoms of schizophrenia, or the other way around? Were the brain differences present at birth or arise during puberty? Does medication that reduces symptoms affect brain structure? We'll consider these questions at length in Chapter 16.

Animal Research Makes Vital Contributions

Because we will draw on animal research throughout this book, we should comment on some of the ethical issues of experimentation on animals. Human beings' involvement and concern with other species pre-dates recorded history. Early humans had to study animal behavior and physiology in order to escape some species and hunt others. To study biological bases of behavior inevitably requires research on animals of other species as well as on human beings.

Because of the importance of carefully regulated animal research for both human and animal health and well-being, the National Research Council (NRC, 1988; NRC, 1991) undertook a study on the many uses of animals in research. The study notes that 93% of the mammals used in research are laboratory-reared rodents. It also reports that most Americans believe that animal research should continue. Of course, researchers have an obligation to minimize the discomfort of their animal subjects, and ironically enough, animal research has provided us with the drugs and techniques to make most research painless for the animal subjects (Sunstein and Nussbaum, 2004).

Nevertheless, a very active minority of people believe that research with animals, even if it does lead to lasting benefits, is unethical. For example, in his 1975 book *Ani-*



(a) Person with schizophrenia

(b) Normal

1.8 Identical Twins but Nonidentical Brains and Behavior In these images of the brains of identical twins, the fluid-filled cerebral ventricle are prominent as dark "butterfly" shapes. The twin whose brain is imaged in (a) suffers from schizophrenia and has the enlarged cerebral ventricles that some researchers believe are characteristic of this disorder. The other twin do not suffer from schizophrenia; his brain (b) clearly has smaller ventricles. (Courtesy of E. Fuller Torrey.)

mal Liberation, Peter Singer asserts that research with animals can be justified only if it actually produces benefits. The trick, of course, is how to predict which experiment will lead to a breakthrough. Although he notes that most experiments do not yield such positive results, Singer has repeatedly refused to say that animal experimentation is never justified (Neale, 2006). In the meantime, animal rights groups have vandalized labs, burned down buildings, and exploded bombs in laboratories—all actions that Singer has condemned.

Psychology students usually underestimate the contributions of animal research to all the main fields of psychology because, as one study found, the most widely used introductory psychology textbooks obscure the contributions of animal research, and they present major findings from animal research as if they were obtained with human subjects (Domjan and Purdy, 1995).

The History of Research on the Brain and Behavior Begins in Antiquity

Only recently have scientists recognized the central role of the brain in controlling behavior. When Egyptian pharaoh Tutankhamen was mummified (about 1300 BCE), four important organs were preserved in alabaster jars in his tomb: liver, lungs, stomach, and intestines. The heart was preserved in its place within the body. All these organs were considered necessary to ensure the pharaoh's continued existence in the afterlife. The brain, however, was removed from the skull and discarded. Although the Egyptian version of the afterlife entailed considerable struggle, the brain was not considered an asset.

Neither the Hebrew Bible (written from the twelfth to the second century BCE) nor the New Testament ever mentions the brain. However, the Bible mentions the heart hundreds of times and makes several references each to the liver, the stomach, and the bowels as the seats of passion, courage, and pity, respectively. "Get thee a heart of wisdom," said the prophet.

The heart is also where Aristotle (about 350 BCE), the most prominent scientist of ancient Greece, located mental capacities. We still reflect this ancient notion when we call people *kindhearted, openhearted, fainthearted, hardhearted,* or *heartless,* and when we speak of learning *by heart.* Aristotle considered the brain to be only a cooling unit to lower the temperature of the hot blood from the heart. Around 400 BCE the great Greek physician Hippocrates was expressing the minority view when he wrote,

> Not only our pleasure, our joy and our laughter but also our sorrow, pain, grief, and tears rise from the brain, and the brain alone. With it we think and understand, see and hear, and we discriminate between the ugly and the beautiful, between what is pleasant and what is unpleasant and between good and evil.

Around 350 BCE, the Greek physician Herophilus (called the "Father of Anatomy") advanced our knowledge of the nervous system by dissecting bodies of both people and animals. Among other investigations, he traced nerves from muscles and skin into the spinal cord. He also noted that each region of the body is connected to separate nerves.

A second-century Greco-Roman physician, Galen (the "Father of Medicine"), treated the injuries of gladiators. His reports of behavioral changes caused by injuries to the heads of gladiators drew attention to the brain as the controller of behavior. Galen advanced the idea that animal spirits—a mysterious fluid—passed along nerves to all regions of the body. But Galen's ideas about the anatomy of the human brain were very inaccurate because he refused to dissect humans.

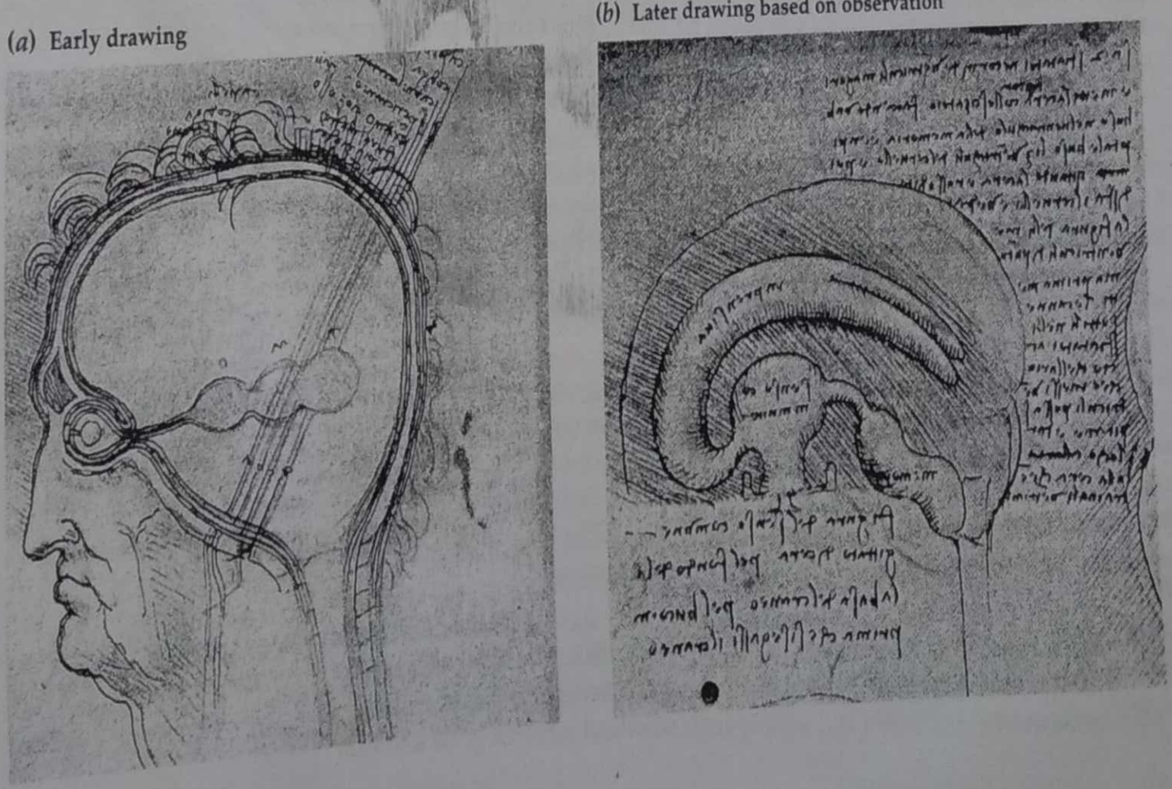
Renaissance scientists began to understand brain anatomy

The eminent Renaissance painter and scientist Leonardo da Vinci (1452–1519) studied the workings of the human body and laid the foundations of anatomical drawing. He especially pioneered in providing views from different angles and cross-sectional representations. His artistic renditions of the body included portraits of the nerves in the arm and the fluid-filled ventricles of the brain (**Figure 1.9**).

Renaissance anatomists emphasized the shape and appearance of the external surfaces of the brain because these were the parts that were easiest to see when the skull was removed. It was immediately apparent to anyone who looked that the brain has an extraordinarily complex shape. To Renaissance artists, this marvelous structure was God's greatest gift to humankind. So, in Michelangelo's painting on the ceiling of the Sistine Chapel, part of which is pictured at the beginning of the chapter, God seems to ride the form of the human brain when bestowing life to Adam.

In 1633, René Descartes (1596–1650) wrote an influential book (*De Homine* [*On Man*]) in which he tried to explain how the behavior of animals, and to some extent the behavior of humans, could be like the workings of a machine. In addition to tackling other topics, Descartes proposed the concept of spinal reflexes and a neural pathway for them (**Figure 1.10**).

Attempting to relate the mind to the body, he suggested that the two come into contact in the pineal gland, located within the brain. He suggested the pineal gland for this role because (1) whereas most brain structures are double, located symmetrically in the



(a) Early drawing

(b) Later drawing based on observation

.9 Leonardo da Vinci's Changing 'iew of the Brain (*a*) In an early rep- esentation, Leonardo simply copied old :hematic drawings that represented the erebral ventricles as a linear series of nambers. (*b*) Later he made a drawing ased on direct observation: after making a ast of the ventricles of an ox brain by ouring melted wax into the brain and let- ng it set, he cut away the tissue to reveal ie true shape of the ventricles.

two hemispheres, the pineal gland is single, like consciousness; and (2) Descartes believed, erroneously, that the pineal gland exists only in humans and not in animals.

As Descartes was preparing to publish his book, he learned that the Pope had forced Galileo to renounce his teaching that Earth revolves around the sun, threatening to execute him if he did not recant. Fearful that his own speculations about mind and body could also incur the wrath of the Church, Descartes withheld his book from publication, and it did not appear in print until 1662, after his death.

Descartes believed that, if people were nothing more than intricate machines, they could have about as much free will as a pocket watch and no opportunity to make the moral choices that were so important to the Church. He asserted that humans, at least, had a nonmaterial soul as well as a material body. This notion of **dualism** spread widely and left other philosophers with the task of determining how a nonmaterial soul could exert influence over a material body and brain. Biological psychologists reject dualism and insist that all the workings of the mind can also, in theory, be understood as purely physical processes in the material world, specifically in the brain.

The concept of localization of function arose in the nineteenth century

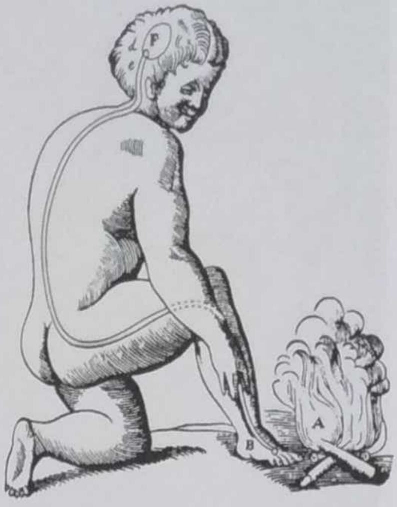
By the end of the 1600s, the English physician Thomas Willis (1621–1675), with his detailed descriptions of the structure of the human brain and his systematic study of brain disorders, convinced educated people in the Western world that the brain is the organ that coordinates and controls behavior (Zimmer, 2004). A popular notion of the nineteenth century, called **phrenology**, elaborated on this idea by asserting that the cerebral cortex consisted of separate functional areas, and that each area was responsible for a behavioral faculty such as love of family, perception of color, or curiosity. Investigators assigned functions to brain regions anecdotally, by observing the behavior of individuals and noting, from the shape of the skull, which underlying regions of the brain were more or less developed (**Figure 1.11*a***).

Opponents rejected the entire concept of localization of brain function, insisting that the brain, like the mind, functions as a whole. Today we know that the whole brain is indeed active when we are doing almost any task. On the other hand, as we saw earlier in this chapter, when we are performing particular tasks, certain brain regions become even more activated. Different tasks activate different brain regions. Modern brain maps of these places where *peaks* of activation occur (**Figure 1.11*b***) bear a passing resemblance to their phrenological predecessors, differing only in the specific locations of functions. But unlike the phrenologists, we confirm these modern maps by other methods, such as examining what happens after brain damage.

Even as far back as the 1860s, the French surgeon Paul Broca (1824–1880) argued that language ability was not a property of the entire brain but rather was localized in a restricted brain region. Broca presented a postmortem analysis of a patient who had been unable to talk for several years. The only portion of the patient's brain that appeared damaged was a small region within the frontal portions of the brain on the left side—a region now known as *Broca's area* (labeled "Speech production" in Figure 1.11*b*). The study of additional patients further convinced Broca that language expression is mediated by this specific brain region rather than reflecting activities of the entire brain.

These nineteenth-century observations form the background for a continuing theme of research in biological psychology—notably, the search for distinguishing differences among brain regions on the basis of their structure, and the effort to relate different kinds of behavior to different brain regions (M. Kemp, 2001). An additional theme emerging from these studies is the relation of brain size to ability (**Box 1.2**).

In 1890, William James's book *Principles of Psychology* signaled the beginnings of a modern approach to biological psychology. The strength of the ideas described in this book is evident by the continuing frequent citation of the work, especially by contemporary cognitive neuroscientists. In James's work, psychological ideas such as consciousness and other aspects of human experience came to be seen as properties of the nervous system. A true biological psychology began to emerge from this approach.

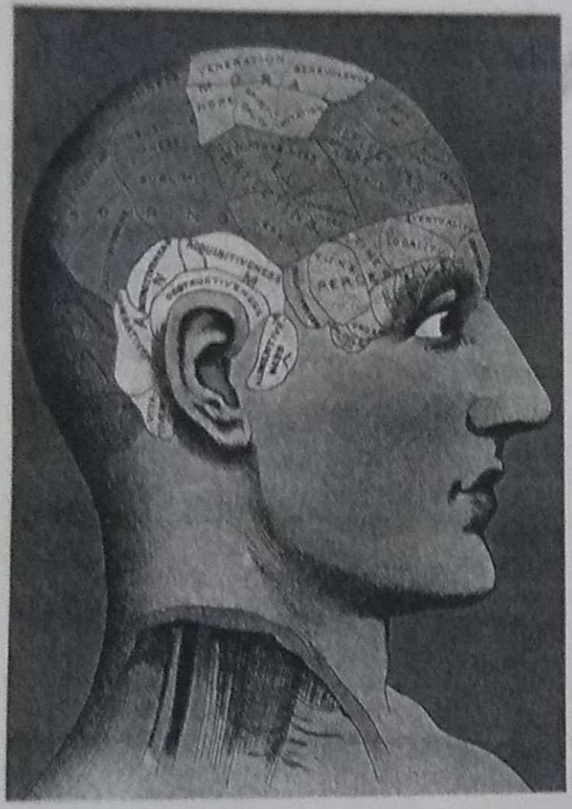


1.10 An Early Account of Reflexes In this depiction of an explanation by Descartes, when a person's toe touches fire, the heat causes nervous activity to flow up the nerve to the brain. There the nervous activity is "reflected" back down to the leg muscles, which contract, pulling the foot away from the fire; the idea of activity being reflected back is what gave rise to the word *reflex*. In Descartes's time, the difference between sensory and motor nerves had not yet been discovered, nor was it known that nerve fibers normally conduct in only one direction. Nevertheless, Descartes promoted thinking about bodily processes in scientific terms, and this focus led to steadily more accurate knowledge and concepts.

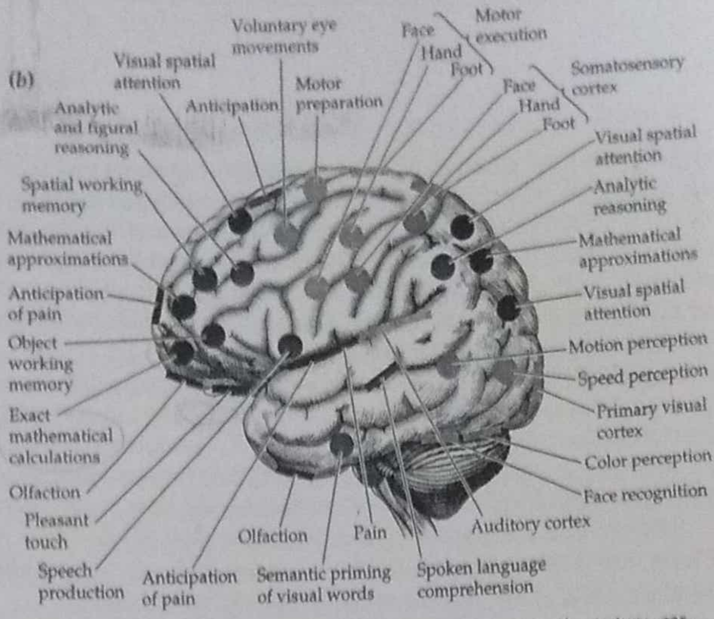
dualism The notion, promoted by Descartes, that the mind is subject only to spiritual interactions, while the body is subject only to material interactions.

phrenology The belief that bumps on the skull reflect enlargements of brain regions responsible for certain behavioral faculties.

(a)

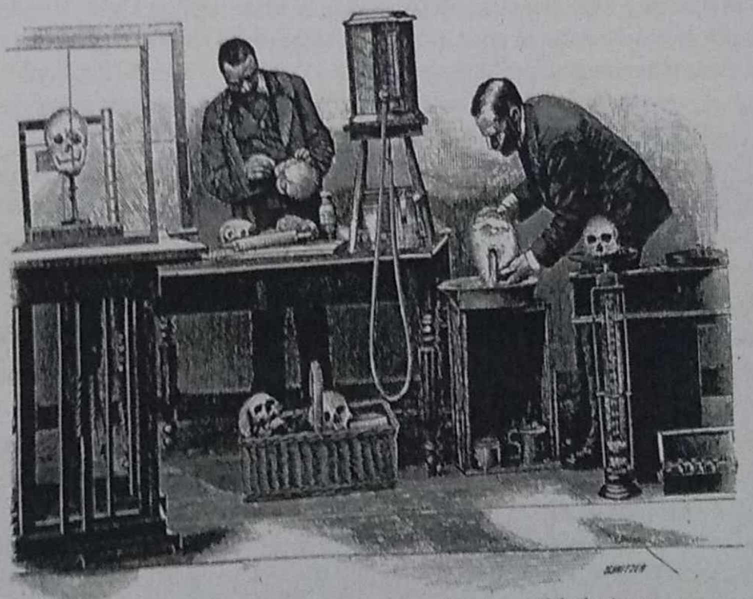


(b)


Voluntary eye movements
Face
Hand
Foot
Motor execution
Visual spatial attention
Motor preparation
Somatosensory cortex
Face
Hand
Foot
Analytic and figural reasoning
Anticipation
Visual spatial attention
Spatial working memory
Analytic reasoning
Mathematical approximations
Mathematical approximations
Anticipation of pain
Visual spatial attention
Object working memory
Motion perception
Speed perception
Exact mathematical calculations
Primary visual cortex
Color perception
Olfaction
Face recognition
Pleasant touch
Auditory cortex
Olfaction
Pain
Speech production
Anticipation of pain
Semantic priming of visual words
Spoken language comprehension

1.11 Old and New Phrenology (*a*) In the early nineteenth century, certain "faculties," such as skill at mathematics or a tendency toward aggression, were believed to be directly associated with particular brain regions. Phrenologists used diagrams like this one to measure bumps on the skull, which they took as an indication of how fully developed each brain region was in an individual, and hence how fully that person should display particular qualities. (*b*) Today, technology allows us to roughly gauge how active different parts of the brain are when a person is performing various tasks (see Chapter 2). But virtually the entire brain is active during any task, so the localization of function that such studies provide is really a measure of where *peak* activity occurs, rather than a suggestion of a single region that is involved in a particular task. (Part *b* after Nichols and Newsome, 1999.)

BOX 1.2 Is Bigger Better? The Case of the Brain and Intelligence



(A) A nineteenth-century apparatus for measuring the volume of the brain case

Does a bigger brain indicate greater intelligence? Brain size does seem to explain many species differences in complex behavior as well as the remarkable expansion of the human brain over the past few million years (see Chapter 6). But do variations in brain size within our species correlate with intelligence? This question has been the subject of lively controversy for at least two centuries. Sir Francis Galton (1822–1911), the scientist who invented the correlation coefficient, stated that the greatest disappointment in his life was his failure to find a significant relationship between head size and intelligence. But Galton had to use head size, when he really wanted to measure brain size. In addition, at the time he undertook this study, there were no good measures of intelligence. Galton had to rely on teachers' estimates of their students' intelligence, and every student knows that teachers can be quite wrong. Other investigators in the nineteenth century measured the volumes of skulls (Figure A) of various groups and estimated intelligence on the basis of people's occupations or other doubtful criteria.

The development and standardization of intelligence tests in the twentieth cen-

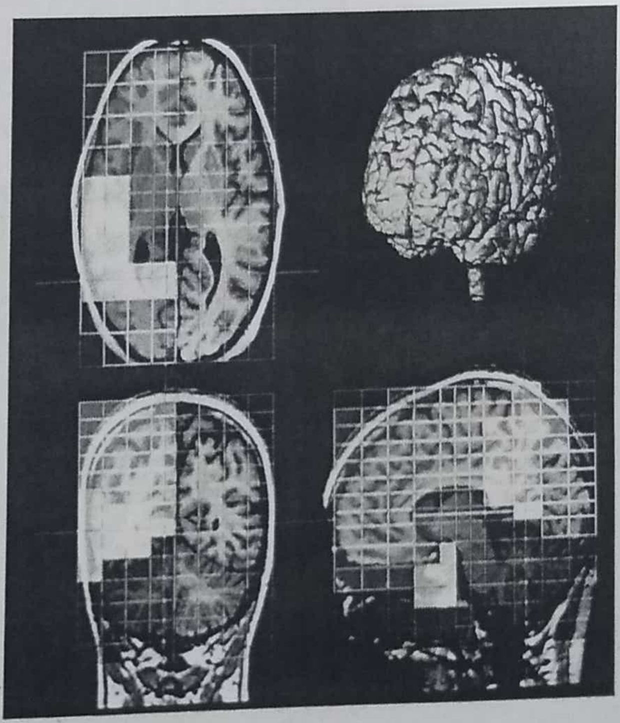
BOX 1.2 (continued)

tury provided invaluable help for one side of the question, but until recently, measures of head size still had to be used to estimate brain size for any sample of living subjects. Such studies usually showed positive but small correlations between brain size and intelligence, with correlations ranging from +0.08 to +0.22 (Van Valen, 1974).

The invention of noninvasive techniques to visualize and measure the brains of living subjects has made possible a direct approach to the question of relations between brain size and intelligence. Brain size is measured for each subject by magnetic resonance imaging (MRI) (this technique is discussed in more detail in Chapter 2); intelligence is measured by standard intelligence quotient (IQ) tests. In one study the overall result was a significant correlation coefficient of about 0.26 (Posthuma et al., 2002). In another study, MRI scans such as those shown in Figure B were used for measuring the sizes of different brain regions. After correction for body size, the correlation between brain size and IQ scores was 0.38 (Andreasen et al., 1993). IQ seems to correlate better with the volume of the front of the brain than the back (Haier et al., 2005). When the brains of children were measured at age 6 and again at 11, those with the highest IQ displayed the greatest thickening of the outer layer of the brain, especially in the front (P. Shaw et al., 2006).

Thus, on the basis of modern techniques, the long-standing controversy appears to have been settled in favor of a significant correlation between brain size and intelligence. Note, however, that the modest size of the correlations, while statistically significant, indicates that only about 10% of variability in IQ is accounted for by brain size. Thus there is plenty of room for other factors to contribute to overall IQ. In addition, many people dispute whether IQ tests really measure a general property of intelligence (Sternberg, 2000).

Historically, scientists have misused information about brain size in racially or ethnically prejudicial ways (S. J. Gould, 1981). In fact, however, all racial groups show overlapping and widely varying intelligence and brain size. (Figure A from the Bettmann Archive; Figure B courtesy of Nancy Andreasen.)



(B) Images from a modern brain measurement study

Modern biological psychology arose in the twentieth century

The end of the nineteenth century brought many important developments for biological psychology. German psychologist Hermann Ebbinghaus showed in 1885 how to measure learning and memory in humans. In 1898, American psychologist Edward L. Thorndike demonstrated how to measure learning and memory in animal. Early in the twentieth century, Russian physiologist Ivan P. Pavlov announced research in his laboratory on conditioning in animals.

American psychologist Shepard I. Franz (1902) sought the site of learning and memory in the brain by removing different brain regions in animal subjects. This work started a search for the traces of experience in the brain—a quest that Karl S. Lashley (1890–1958) referred to as the "search for the engram." Lashley studied with Franz and took over the problem of investigating the locations and mechanisms of memory functions in the brain. In a long career, Lashley contributed many important findings and trained many students to study the biological mechanisms not only of learning and memory, but also of perception and motivation.

consciousness The state of awareness of one's own existence and experience.

Biological psychology bears the strong imprint of Canadian psychologist Donald O. Hebb (1904–1985), a student of Lashley (P. M. Milner, 1993). In his book *The Organization of Behavior* (1949), Hebb showed in principle how complex cognitive behavior could be accomplished by networks of active neurons. He suggested how brain cell connections that are initially more or less random could become organized by sensory input and stimulation into strongly interconnected groups that he called *cell assemblies*. His hypothesis about how neurons strengthen their connections through use became known as the *Hebbian synapse*, a topic much studied by current neuroscientists (see Chapter 18).

Consciousness is a thorny problem

Almost anyone using this book has at some time wondered about **consciousness**: the personal, private awareness of our emotions, intentions, thoughts, and movements, and of the sensations that impinge upon us. How is it possible that you are aware of the words on this page, the room you are occupying, the goals you have in life?

In his review of theories of consciousness, Adam Zeman (2002) notes that almost all scientists agree on some aspects of consciousness:

- Consciousness matters; it permits us to do certain important things, like planning and mentally "simulating" what might happen in the future.
- Consciousness is bound up somehow with the activity of the brain.
- We are not aware of all of our brain's activities. Some brain activity, and therefore some of our behavior, is unconscious.
- The deepest parts of our brain are important for arousal.
- The topmost parts of the brain are responsible for whatever we experience from moment to moment.

In the chapters to come, we will see many examples of experiments that demonstrate these properties of consciousness. However consciousness is brought about, any satisfying understanding would be able, for example, to explain why a certain pattern of activity in your brain causes you to experience the sensation of blue when looking at the sky, or the smell of cinnamon when entering a bakery. A good theory would let us predict that, by messing about with your brain, changing particular connections or activating particular neurons, you would now experience yellow when seeing the sky (and it's not fair to put colored goggles in front of your eyes; that's easy to understand). Unfortunately, we are nowhere near understanding consciousness this clearly. Thus, in the rest of this book we will rarely use the words *conscious* or *consciousness*. Normally we cannot say anything about the particulars of what human or animal subjects are *experiencing*, but only whether their behavior suggests that the brain detected a signal or event. So we are in no position to know whether complicated machines like computers are, or might one day be, conscious.

Some people even doubt whether our "merely human" brains will ever be able to understand something as complicated as consciousness. Nevertheless, any gains we make in understanding how the brain works, which is the subject of this book, will get us closer to that goal.

Recommended Reading

Blackmore, S. (2004). *Consciousness: An introduction.* New York: Oxford University Press.

Finger, S. (1994). *Origins of neuroscience.* New York: Oxford University Press.

Gallagher, S. (2006). *How the body shapes the mind.* New York: Oxford University Press.

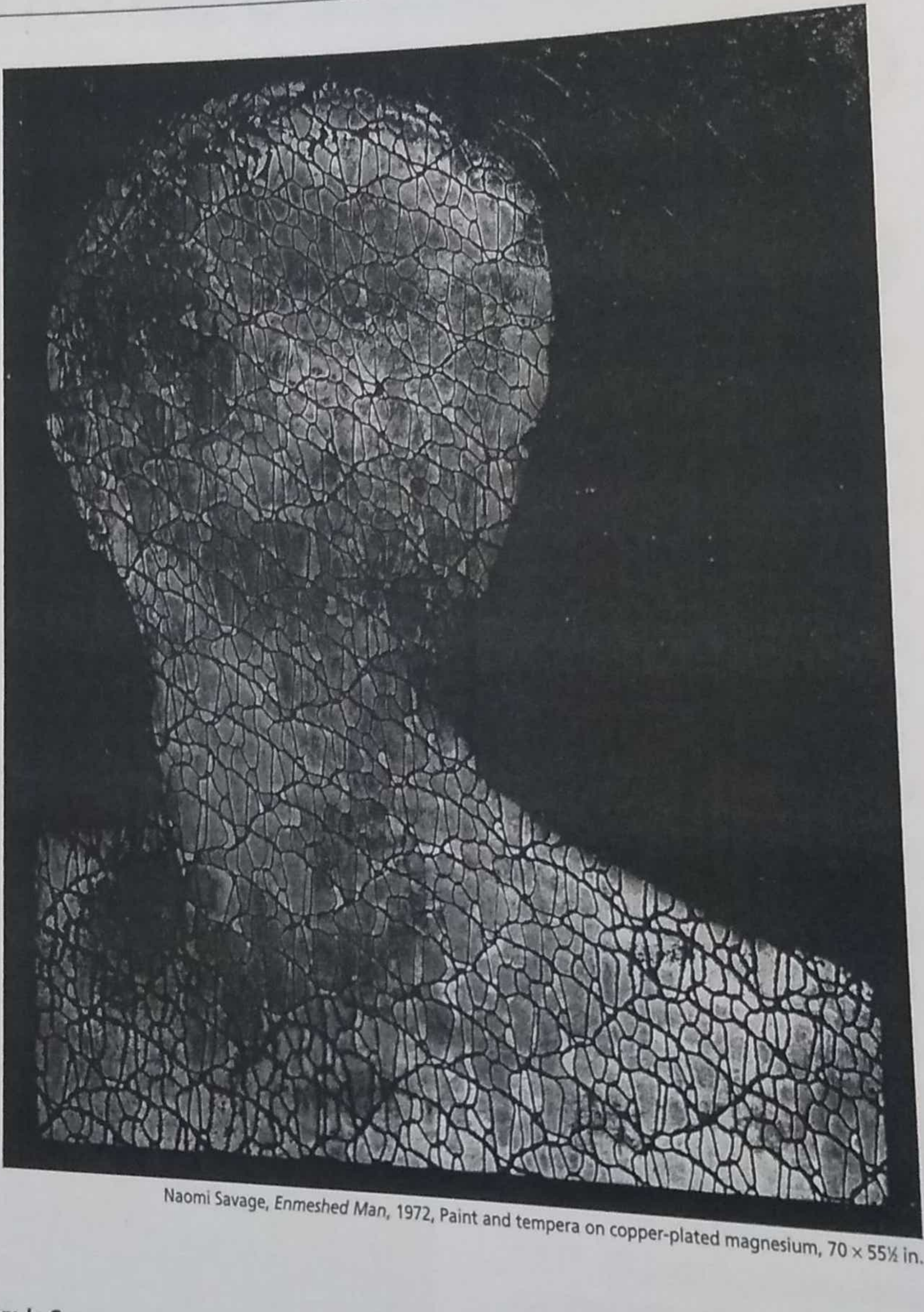
Howard, P. J. (2000). *Owner's manual for the brain: Everyday applications from mind-brain research* (2nd ed.). Austin, TX: Bard Press.

Pechura, C. M., and Martin, J. B. (Eds.). (1991). *Mapping the brain and its functions.* Washington, DC: National Academy Press.

Zimmer, C. (2004). *The soul made flesh: The discovery of the brain—and how it changed the world.* New York: Basic Books.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

CHAPTER 2



Naomi Savage, *Enmeshed Man*, 1972, Paint and tempera on copper-plated magnesium, 70 × 55½ in.

CONTENTS

The Nervous System Is Composed of Cells 23

The Nervous System Consists of Central and Peripheral Divisions 34

The Brain Is Described by Both Structure and Function 44

Specialized Support Systems Protect and Nourish the Brain 49

Newer Imaging Techniques Allow Us to Look into the Living Human Brain 51

Functional Neuroanatomy: The Nervous System and Behavior

Mapping the Human Brain

It's like a scene from a science fiction film: While you remain conscious and aware of your surroundings, the surface of your brain is exposed and electrically stimulated in precise locations, and your behavioral responses are carefully noted. With procedures perfected during the mid-twentieth century by neurosurgeon Wilder Penfield (1891–1976) , thousands of people have undergone electrical-stimulation mapping of the brain to guide the removal of diseased brain tissue without encroaching on neighboring regions critical for important functions like speech or movement. But Penfield and others realized that, beyond its utility as a surgical tool, stimulation mapping offered a way to ask more-profound questions about the organization of the brain.

Penfield found that stimulation of some brain regions reliably provoked specific movements, whereas stimulation of other regions produced specific sensations, like a tingling hand or flashes of blue light. Elsewhere, stimulations could evoke clear and nuanced vignettes of past experiences, such as the smell of a childhood haunt, or a fragment of a favorite song. Some regions were organized identically in different individuals; other regions defied attempts to create functional maps that could be generalized to other people.

Although we now know quite a bit about the organization of basic functions, the brain's control of complex cognition remains mostly a tantalizing mystery. However, the advent of sophisticated brain-imaging technology has infused new vigor into the search for answers to fundamental questions about brain organization.

Does each brain region control a specific behavior? Conversely, can every behavior be linked to a particular brain region? Or do some regions act as general-purpose processors? How do the brains of men and women differ? Is everybody's brain organized in the same way?

Thoughts, feelings, perceptions, and acts—from the simplest movements to the most complex ideas—these are the products of the three-pound organ inside your head. In this chapter we begin our exploration of the physiological substrates of behavior by surveying the structure and basic functioning of this most complicated object. Neuroscientists adopt several different perspectives in describing the physical properties of the brain: accordingly, we open by introducing its microscopic, cellular anatomy—its **histology**. We then turn to **gross neuroanatomy**: the larger-scale neural structures, apparent to the naked eye, that are constructed from cellular building blocks.

In Chapter 3 we will delve more deeply into the workings of nerve cells (generally referred to as **neurophysiology**), especially the creation and transmission of the electrochemical signals that convey information. Chapter 4 will extend our discussion of neural activity by describing the **chemical neuroanatomy** of the brain (the chemical systems that nerve cells use to communicate) and will review the experimental, medical, and recreational use of chemicals to change the functioning of the nervous system—a field known as **neuropharmacology**. Chapter 5 will conclude our survey of the structure and function of the nervous system by discussing the hormonal interface between the nervous system and the rest of the body.

The Nervous System Is Composed of Cells

The nervous system extends throughout the body, contacting every organ and muscle. Like all living tissue, the nervous system is made up of cells, the most important

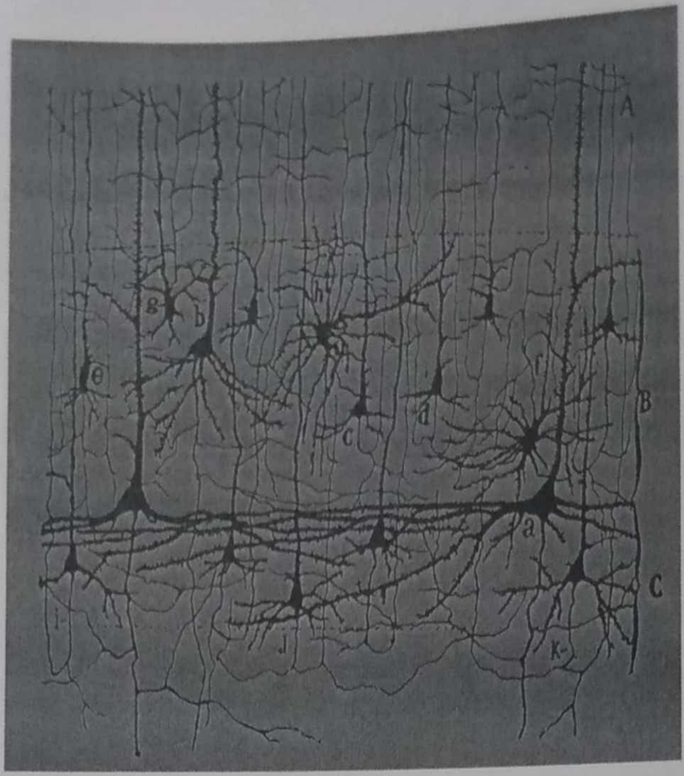
histology The study of tissue structure.

gross neuroanatomy Anatomical features of the nervous system that are apparent to the naked eye.

neurophysiology The study of the life processes of neurons.

chemical neuroanatomy The distribution of key chemicals, such as transmitters and enzymes, within the structure of the nervous system.

neuropharmacology Also called *psychopharmacology*. The study of the effects of drugs on the nervous system and behavior.



2.1 Nineteenth-Century Drawings of Neurons The great Spanish neuroanatomist, Santiago Ramón y Cajal, created detailed renderings of the cells of the nervous system; the image here was the inspiration for this book's cover.

of which are the **nerve cells**, or **neurons**. The assembly of these cellular building blocks into circuits is what underlies the simplest and the most complex of our abilities and talents. Each neuron receives inputs from many other nerve cells, integrates those inputs, and then distributes the processed information to other neurons. This is the vital job that your brain must accomplish: the integration and analysis of information.

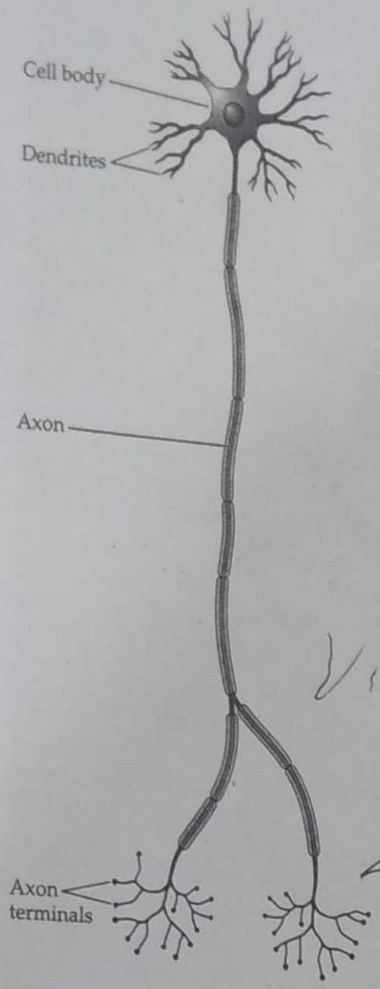
Understanding the genetic guidance of the construction of the brain is one of the key goals of twenty-first-century neuroscience (Boguski and Jones, 2004) and the topic of Chapter 7. For now, just consider that, while we have only about 30,000 genes, our brains contain 100 billion to 150 billion neurons, making approximately 10^{15} connections with one another! That vast network is responsible for all of humanity's achievements, so we'll begin with neurons and how they're connected.

The neuron doctrine defines neurons and their connections

In the late nineteenth century, anatomists sought to understand the differences between human and animal brains by using microscopes to study brain cells. Using special stains to make the normally transparent cells visible, they found that brains contain a large assembly of oddly shaped neurons. Unlike the cells of other organs, neurons are enormously varied in size and form.

The interconnection of nerve cells was a hotly debated question in the early days of modern neuroscience. Some nineteenth-century anatomists, notably Italian anatomist Camillo Golgi (1843–1926), thought that neurons were continuous with one another, forming a nearly endless network of connected tubes through which information flowed. But Spanish anatomist Santiago Ramón y Cajal (1852–1934), using Golgi's revolutionary staining techniques (see Box 2.1), developed a convincing alternative. On the basis of elegant studies of neurons, drawn so precisely that they remain accurate and useful to the present day (**Figure 2.1**), Cajal argued that although neurons come very close to one another (i.e., they are *contiguous*), they are not quite *continuous* with one another. He insisted that at each point of contact between neurons is a tiny gap that keeps the cells separate.

neuron or nerve cell The basic unit of the nervous system, each composed of a cell body, receptive extension(s) (dendrites), and a transmitting extension (axon).



2.2 The Major Parts of the Neuron

From these studies emerged a new perspective—the **neuron doctrine**—which stated that (1) the brain is composed of separate neurons and other cells that are independent structurally, metabolically, and functionally; and (2) information is transmitted from cell to cell across tiny gaps. These gaps were later demonstrated by Sir Charles Sherrington (1857–1957), who named them **synapses**. By the 1950s, the high-resolution abilities of the electron microscope had fully confirmed the neuron doctrine. Nerve cells are indeed separate from each other.

Another important class of cells in the nervous system consists of the **glial cells** (sometimes called *glia* or *neuroglia*). Evidence is mounting that glial cells are important participants in information processing, but because neurons are generally larger and produce readily measured electrical signals, we know much more about them than about glial cells.

The neuron has four structural divisions specialized for information processing

The typical neuron collects signals from several sources, integrates this information, and distributes the processed information to other cells by means of its own electrochemical output signals. Because they are cells, neurons contain the usual cellular components that are common to all cells of the body, including **mitochondria** (singular *mitochondrion*) that produce energy, the **cell nucleus** that contains genetic instructions, and the **ribosomes** and related machinery that translate genetic instructions into proteins. In addition, however, all neurons share some distinctive structural parts that are directly related to information processing. These parts, illustrated in **Figure 2.2**, represent four functional zones (see Figure 2.5):

1. *Input zone.* Cellular extensions called **dendrites** (from the Greek *dendron*, "tree") serve as an **input zone**, receiving information from other neurons. Dendrites may be elaborately branched, to accommodate contacts from many other neurons.
2. *Integration zone.* A **cell body** region (or **soma**, plural *somata*), which contains the cell's nucleus, may receive additional synaptic contacts. In most types of neurons, inputs are combined and transformed by specialized structures that serve as an **integration zone**. This zone is typically part of the cell body.
3. *Conduction zone.* A single extension, the **axon**, leads away from the cell body and serves as a **conduction zone**, transmitting the cell's electrical impulse away from the cell body.
4. *Output zone.* Specialized swellings at the ends of the axon, the **axon terminals** (sometimes called *synaptic boutons*), are a functional **output zone**. They communicate the cell's activity to other cells.

In many neurons the axon is only a few micrometers (μm) long, but for the neurons that connect the spinal cord to the rest of the body, axons may reach more than a me-

neuron doctrine The hypothesis that the brain is composed of separate cells that are distinct structurally, metabolically, and functionally.

synapse A cellular location at which information is transmitted from one neuron to another.

glial cells Also called *glia* or *neuroglia*. Nonneural brain cells that provide structural, nutritional, and other types of support to the brain.

mitochondrion A cellular organelle that provides metabolic energy for the cell's processes.

cell nucleus The spherical central structure of a cell that contains the chromosomes.

ribosomes Structures in the cell body where genetic information is translated (proteins are produced).

dendrite One of the extensions of the cell body that are the receptive surfaces of the neuron.

input zone The part of a neuron that receives information, from other neurons or from specialized sensory structures. Usually corresponds to the cell's dendrites.

cell body or soma The region of a neuron that is defined by the presence of the cell nucleus.

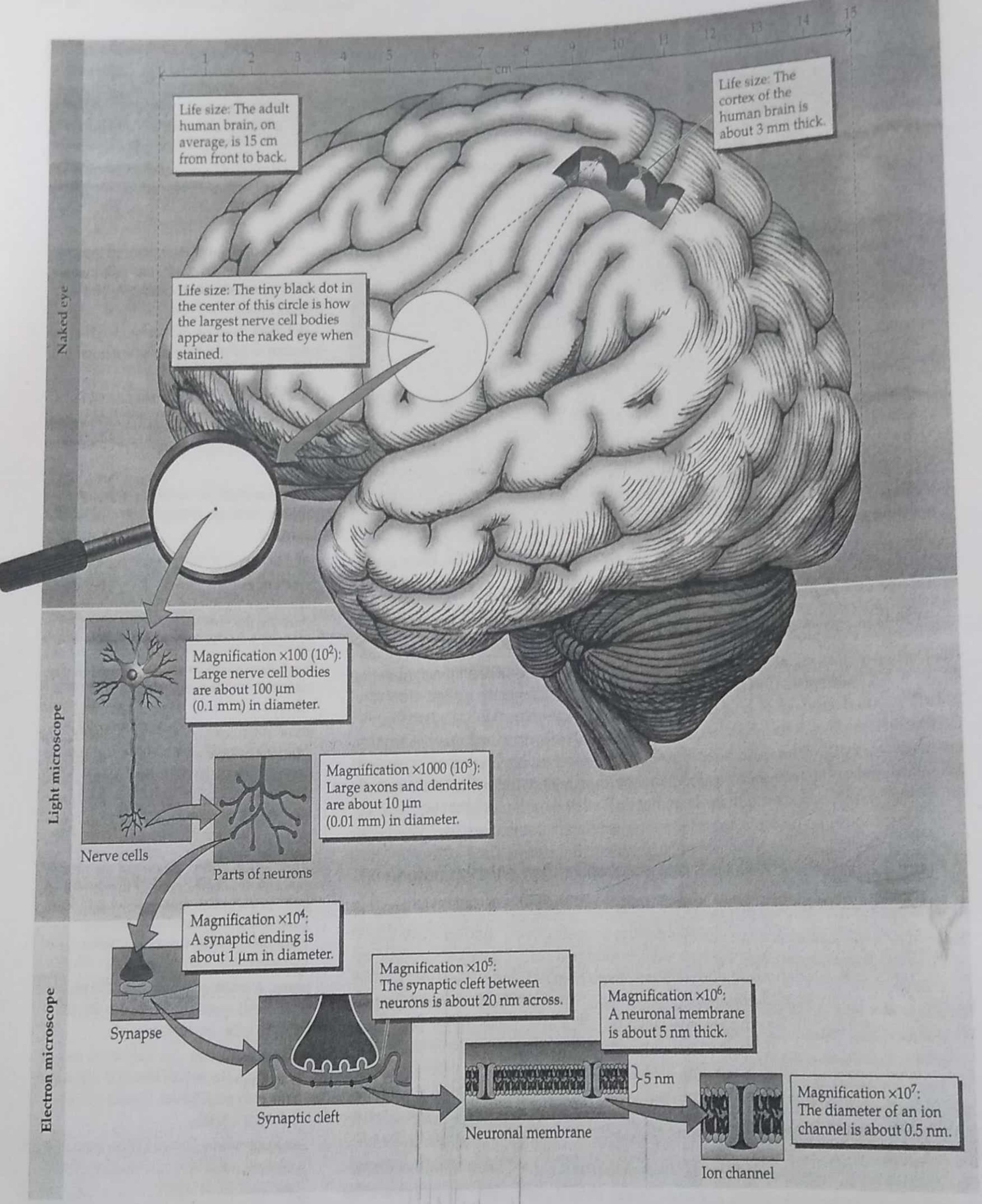
integration zone The part of the neuron that initiates nerve activity if the sum of all inhibitory and excitatory postsynaptic potentials exceeds a threshold value. Usually corresponds to the neuron's axon hillock.

axon A single extension from the nerve cell that carries nerve impulses from the cell body to other neurons.

conduction zone The part of the neuron over which the nerve's electrical signal may be actively propagated. Usually corresponds to the cell's axon.

axon terminal The end of an axon or axon collateral, which forms a synapse on a neuron or other target.

output zone The part of a neuron, usually corresponding to the axon terminals, at which the cell's electrical activity is conveyed to another cell.



Life size: The adult human brain, on average, is 15 cm from front to back.

Life size: The cortex of the human brain is about 3 mm thick.

Life size: The tiny black dot in the center of this circle is how the largest nerve cell bodies appear to the naked eye when stained.

Magnification ×100 (10^2): Large nerve cell bodies are about 100 μm (0.1 mm) in diameter.

Magnification ×1000 (10^3): Large axons and dendrites are about 10 μm (0.01 mm) in diameter.

Magnification ×10^4: A synaptic ending is about 1 μm in diameter.

Magnification ×10^5: The synaptic cleft between neurons is about 20 nm across.

Magnification ×10^6: A neuronal membrane is about 5 nm thick.

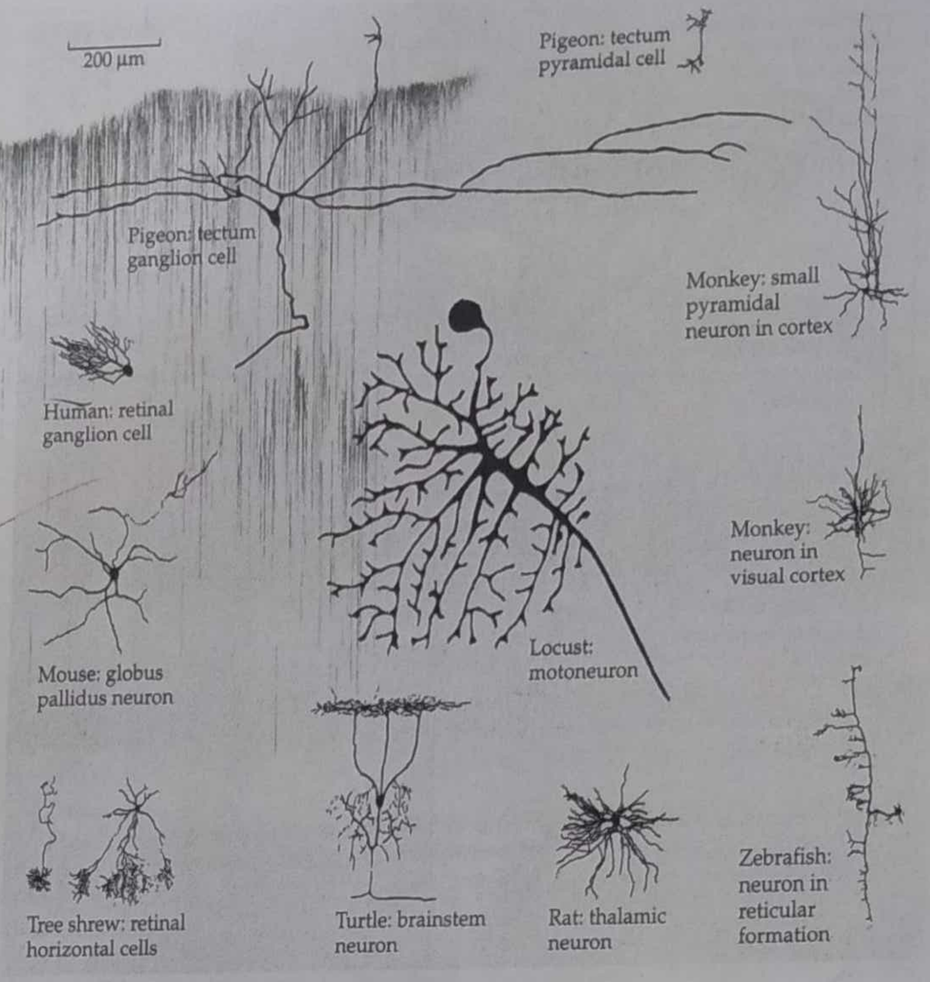
Magnification ×10^7: The diameter of an ion channel is about 0.5 nm.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
cm
Naked eye
Light microscope
Electron microscope
Nerve cells
Parts of neurons
Synapse
Synaptic cleft
5 nm
Neuronal membrane
Ion channel

2.3 Sizes of Some Neural Structures and the Units of Measure and Magnification Used in Studying Them

ter in length.* For example, the giraffe has axons that are, incredibly, several meters long. In order for you to wiggle your toes, individual axons must carry the instructions from the spinal cord to muscles in your foot. Long fibers of sensory neurons then carry messages back to the spinal cord. The relative sizes of some of the neural structures that we will be discussing throughout the book are illustrated in **Figure 2.3**.

Neurons are remarkably diverse in shape; at least 200 geometrically distinguishable types of nerve cells are found in the brains of mammals. **Figure 2.4** offers a small sample of the many different shapes that neurons may take. These differences in size and shape reflect the different ways in which neurons process and transmit information. Although their small size and complexity make the cells of the nervous system difficult to study, a variety of techniques have been developed to help us visualize their structure and activities. Some of these are described in **Box 2.1**.


200 μm
Pigeon: tectum pyramidal cell
Pigeon: tectum ganglion cell
Monkey: small pyramidal neuron in cortex
Human: retinal ganglion cell
Monkey: neuron in visual cortex
Mouse: globus pallidus neuron
Locust: motoneuron
Tree shrew: retinal horizontal cells
Turtle: brainstem neuron
Rat: thalamic neuron
Zebrafish: neuron in reticular formation

2.4 Variety in the Form of Nerve Cells Note the considerable variety in the shape and size of these neurons (drawn to scale) from the brain or spinal cord of different animals.

Neurons can be classified by shape, size, or function

Anatomists use the shapes of cell bodies, dendrites, and axons to classify the many varieties of nerve cells into three principal types, each specialized for a particular kind of information processing.

1. **Multipolar neurons** have many dendrites and a single axon, and they are the most common type of neuron (**Figure 2.5*a***).
2. **Bipolar neurons** have a single dendrite at one end of the cell and a single axon at the other end (**Figure 2.5*b***). This type of neuron is especially common in sensory systems, such as the retina.
3. **Monopolar neurons** have a single extension (or *process*), usually thought of as an axon, that branches in two directions after leaving the cell body (**Figure 2.5*c***). One end is the receptive pole (the input zone); the other, the output zone. Such cells transmit touch information from the body into the spinal cord.

In all three types of neurons, the dendrites are in the input zone; and in multipolar and bipolar cells, the cell body also is part of the input zone.

Another common way of classifying nerve cells is by size. Vertebrate nerve cell bodies range from as small as 10 μm to as large as 100 μm or more in diameter; the diversity in neuronal sizes is evident in Figure 2.4. Larger neurons tend to have more-complex inputs and outputs, cover greater distances, and/or convey information more rapidly than smaller neurons.

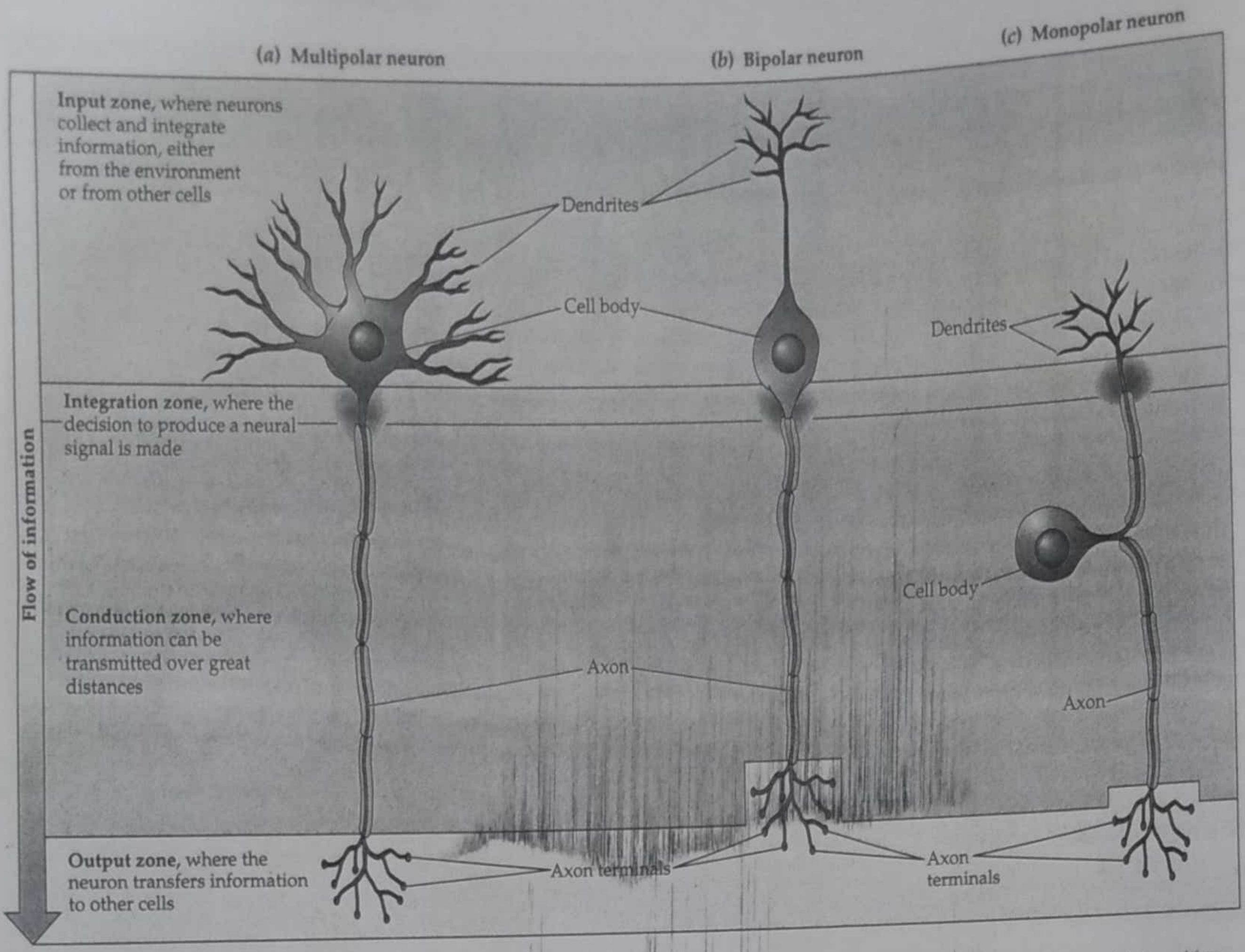
multipolar neuron A nerve cell that has many dendrites and a single axon.

bipolar neuron A nerve cell that has a single dendrite at one end and a single axon at the other end.

monopolar neuron A nerve cell with a single branch that leaves the cell body and then extends in two directions: one end is the receptive pole, the other end the output zone.

---

* The meter (m), the basic unit of length in the metric system, equals 39.37 inches. A centimeter (cm) is one-hundredth of a meter (10^{-2} m); a millimeter (mm) is one-thousandth of a meter (10^{-3} m); a micrometer, or micron (μm), is one-millionth of a meter (10^{-6} m); and a nanometer (nm) is one-billionth of a meter (10^{-9} m).


(a) Multipolar neuron
(b) Bipolar neuron
(c) Monopolar neuron
Input zone, where neurons collect and integrate information, either from the environment or from other cells
Dendrites
Cell body
Dendrites
Integration zone, where the decision to produce a neural signal is made
Flow of information
Cell body
Conduction zone, where information can be transmitted over great distances
Axon
Axon
Output zone, where the neuron transfers information to other cells
Axon terminals
Axon terminals

2.5 A Classification of Neurons into Three Principal Types (*a*) A multipolar neuron has many dendrites extending from the cell body, and a single axon. (*b*) A bipolar neuron has a single dendrite extending from the cell body, and a single axon. (*c*) A monopolar neuron has a single branch that emerges from the cell body and extends in two directions. Note the four functional zones (input, integration, conduction, and output), which are common to all neurons.

A third way to classify neurons is by function. For example, the axon terminals of **motoneurons** (*motor neurons*) contact muscles or glands, providing a pathway for the brain and spinal cord to control body movements and organ function. Other neurons are directly affected by environmental stimuli; they respond to light, a particular odor, or touch. These cells are **sensory neurons**. The remaining neurons, which constitute the vast majority, receive input from and send their output to other neurons; thus they are called **interneurons**.

Some glial cells support neural activity

Glial cells (**Figure 2.6**) were originally believed to hold the nervous system together (the Greek *glia* means "glue"). Clearly, structural support is one biological role of glial cells. But glial cells can also communicate with each other and with neurons, and they can directly affect neuronal functioning by providing neurons with raw materials and chemical signals that alter neuronal structure and excitability. In its exclusion of glial cells, the neuron doctrine was perhaps an oversimplification (Bullock et al., 2005).

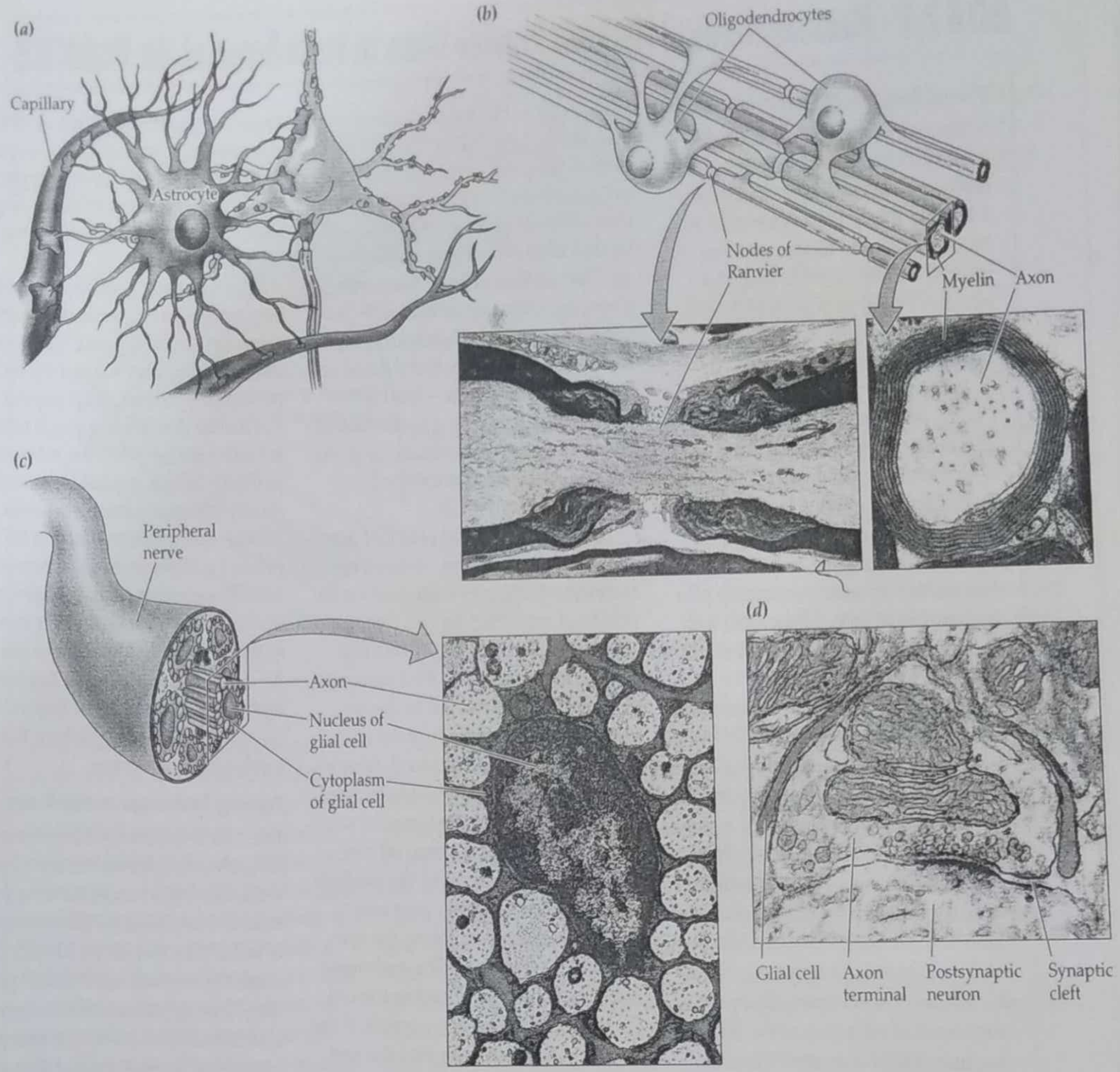
Compared to the hundreds of types of neurons, glial cells come in only four basic forms. One type, called an **astrocyte** (from the Greek *astron*, "star"), is a star-shaped cell with numerous processes in all directions (**Figure 2.6a**), weaving among neurons and

motoneuron Also called *motor neuron*. A nerve cell in the spinal cord that transmits motor messages from the spinal cord to muscles.

sensory neuron A neuron that is directly affected by changes in the environment, such as light, odor, or touch.

interneuron A neuron that is neither a sensory neuron nor a motoneuron; it receives input from and sends output to other neurons.

astrocyte A star-shaped glial cell with numerous processes (extensions) that run in all directions.


(a)
Capillary
Astrocyte
(b)
Oligodendrocytes
Nodes of Ranvier
Myelin
Axon
(c)
Peripheral nerve
Axon
Nucleus of glial cell
Cytoplasm of glial cell
(d)
Glial cell
Axon terminal
Postsynaptic neuron
Synaptic cleft

2.6 Representative Glial Cells (*a*) One type of astrocyte—the protoplasmic astrocyte—contacts capillaries and is adjacent to nerve cell membranes. (*b*) Extensions of oligodendrocytes form myelin wrapping (blue) on axons (yellow); four axons are shown in this view. The colorized electron micrograph of a myelinated axon (*right*) shows the many layers of the myelin sheath. The longitudinal micrograph of an axon (*left*) shows a node of Ranvier, the gap between adjacent myelinated segments. (*c*) Axons that lack this wrapping, called *unmyelinated axons*, are embedded in the troughs of glial cells. In the magnified cross section shown here, the light-colored circular shapes are unmyelinated axons. The large dark area in the center of the photograph is the nucleus of a glial cell, the cytoplasm of which surrounds the axons. (*d*) Processes from astrocytes (blue) surround and insulate synapses, and directly modify synaptic activity. (Micrographs *b* [*left*] and *d* courtesy of Mark Ellisman and the National Center for Microscopy and Imaging Research; *b* [*right*] and *c* from Peters et al., 1991.)

axons. Some astrocytes form suckerlike end feet on blood vessels of the brain, and may serve as a conduit between the vascular system and the brain. Synaptic signaling, the formation of new synapses, and the dynamic control of local blood flow are all directly coordinated by neurons and astrocytes working together. Although astrocytes are not

BOX 2.1 Neuroanatomical Methods Provide Ways to Make Sense of the Brain

Visualizing Structures in the Brain

In the mid-1800s, dyes used to color fabrics provided a breakthrough in anatomical analysis. Preserved nerve cells treated with these *stains* suddenly become vivid, and hidden parts become evident. Different dyes have special affinities for different parts of the cell, such as membranes, the cell body, or the sheaths surrounding axons.

Golgi stains fill the whole cell, including details such as dendritic spines (Figure A). Golgi staining is often used to characterize the variety of cell types in a region. For reasons that remain a mystery, this technique stains only a small number of cells, each of which stands out in dramatic contrast to adjacent unstained cells. Filling a cell with fluorescent molecules is a modern alternative (Figure B).

Nissl stains outline all cell bodies because the dyes are attracted to RNA, which encircles the nucleus. Nissl stains allow us to measure cell body size and the density of cells in particular regions (Figure C). Other stains are absorbed by myelin, the fatty sheaths that surround some axons (see, for example, the sections of spinal cord shown in Figure 2.10). Improved light microscopes and electron microscopy have also broadened our understanding of the fine structure of cells (e.g., see Figures 2.6 and 2.7).

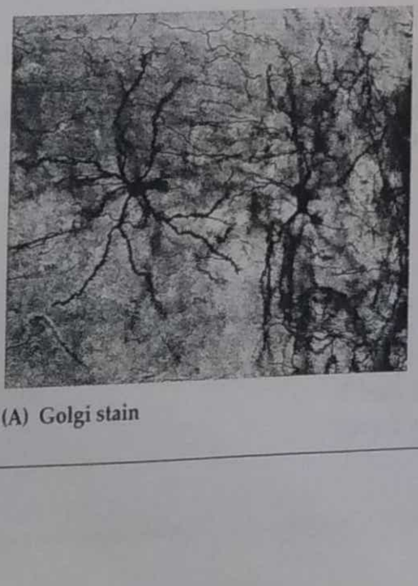
In a procedure known as **autoradiography**, cells are manipulated into taking photographs of themselves. For example, in order to identify the parts of the brain that are affected by a newly discovered drug, experimenters might inject animals with a radioactively labeled form of the drug. Time is then allowed for the radioactive drug to reach its target. Thin sections of brain tissue are placed on slides and covered with photographic emulsion. Radioactivity emitted by the labeled drug in the tissue "exposes" the emulsion—like light striking film—producing a collection of fine, dark grains wherever the drug has become selectively concentrated (see Box 5.1 and Figure 14.3).

Another way to label cells that have an attribute in common—termed **immunocytochemistry**—capitalizes on the affinity of antibodies for specific proteins. Brain slices are exposed to antibodies that are selective for a particular cellular protein of interest to the researchers (it is possible to make antibodies for almost any protein). After allowing time for the antibodies to attach to molecules of the target protein, unattached antibodies are rinsed off and chemical treatments make the antibodies visible. The process reveals only those cells that were making the specific protein (Figure D). This technique can even tell us where, within the cell, the protein is found. For example, if the protein is a neurotransmitter, the antibodies will detect it in axon terminals. A conceptually related procedure called **in situ hybridization** (Figure E) goes a step further and, using radioactively labeled lengths of nucleic acid (RNA or DNA), identifies neurons that contain a specific mRNA message (see the appendix). This is equivalent to identifying the cells in which a gene of interest has been turned on.

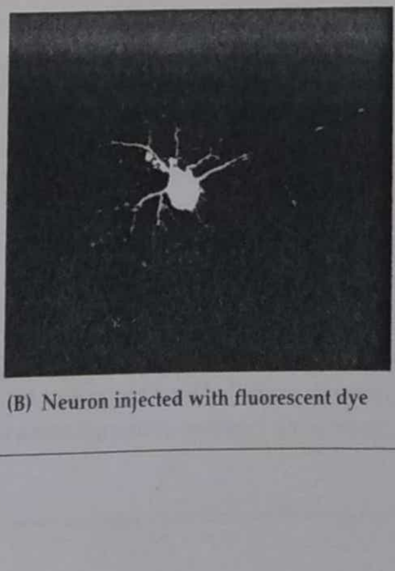
When neurons become more active, they tend to express **immediate early genes (IEGs)**, such as ***c-fos***. Using immunocytochemistry to label the IEG product has become a very popular method for determining which neurons are active during particular behaviors. In this technique, animals are sacrificed shortly after performing a behavior of interest, and the distribution of IEG product in brain slices taken from these animals corresponds to the regions of the brain that were most likely involved in that behavior (Figure F). The use of IEG immunocytochemistry has largely replaced older techniques that used radioactive versions of metabolic fuels to localize brain activation.

Tracing Pathways in the Brain

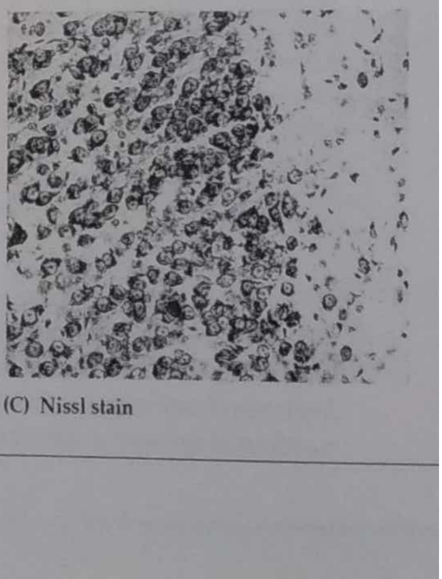
The cells of the brain are interconnected through a complex web of axonal pathways. Gaining an understanding of neuronal circuitry required the development of techniques that clearly identify the origins or destinations of neural pathways. Tracing pathways in the nervous system is difficult for several reasons: (1) axons have an even smaller diameter than cell bodies; (2) axons from different sources look alike; (3) the brain contains billions of axons; and (4) fibers with different destinations often travel together



(A) Golgi stain

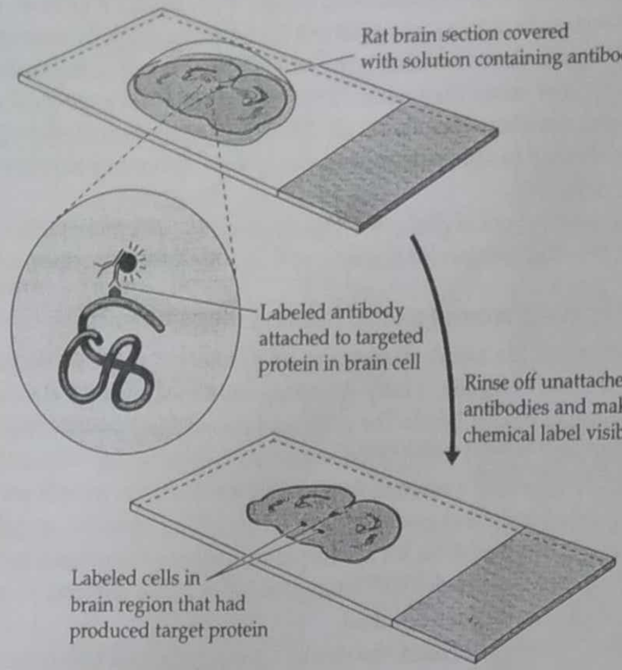


(B) Neuron injected with fluorescent dye



(C) Nissl stain

BOX 2.1 (continued)



(D) Immunocytochemistry

over parts of their routes, making it hard to disentangle one set from the rest.

Classic anatomical techniques for tracing pathways rely on visualization of the products of degenerating axons. Newer procedures accomplish the same goal by the injection of radioactively labeled amino acids into a collection of cell bodies. These radioactive molecules are taken up by the cell, incorporated into proteins, and transported to the tips of the axons (this process is termed *anterograde labeling*). Autoradiographic procedures, as described earlier in this box, are then used to visualize the locations of the transported substances, making the whole pathway known.

A powerful technique for determining the cells of origin of a particular set of axons employs a tracer such as **horseradish peroxidase** (**HRP**), an enzyme found in the roots of horseradish. HRP acts as a tracer of pathways because it is taken up into the axon at the terminals and transported back to the cell body. After HRP is injected into one part of the nervous system, any neurons that have axon terminals there transport the HRP back to the cell body (this process is termed *retrograde labeling*), which can be made visible by means of certain chemical reactions (Figure G). All along the way, visible reaction products are formed—akin to footprints along a pathway. (Figure A courtesy of Timothy DeVoogd; B courtesy of Carla Shatz; E courtesy of Brian Sauer and Suzanne Pham; Figure G courtesy of Dale Sengelaub.)

Golgi stain A histological stain that fills a small proportion of neurons with a dark, silver-based precipitate.

Nissl stain A histological stain that outlines all cell bodies because the dyes are attracted to RNA, which encircles the nucleus.

autoradiography A histological technique that shows the distribution of radioactive chemicals in tissues.

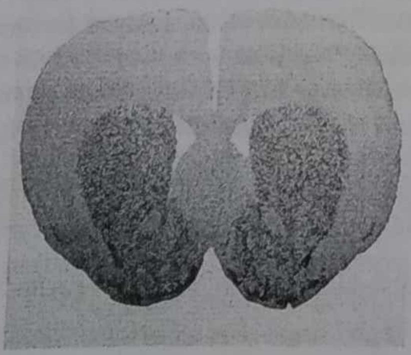
immunocytochemistry (ICC) A method for detecting a particular protein in tissues in which (1) an antibody recognizes and binds to the protein and (2) chemical methods are then used to leave a visible reaction product around each antibody.

in situ hybridization A method for detecting particular RNA transcripts in tissue sections by providing a nucleotide probe that is complementary to, and will therefore hybridize with, the transcript of interest.

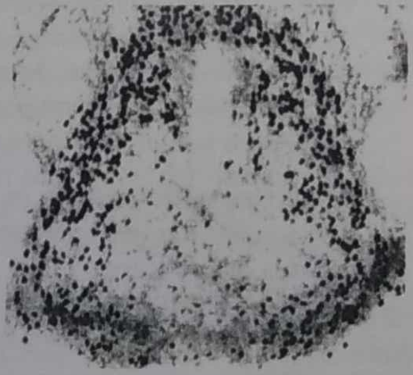
immediate early genes (IEGs) A class of genes that show rapid but transient increases in expression in cells that have become activated.

c-fos An immediate early gene commonly used to identify activated neurons.

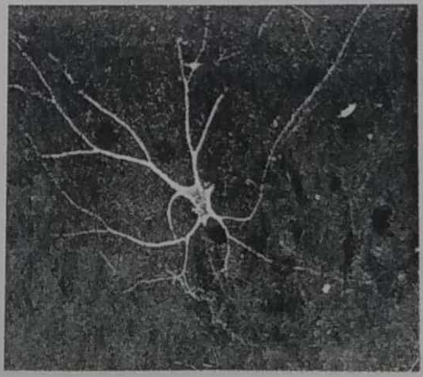
horseradish peroxidase (HRP) An enzyme found in horseradish and other plants that is used to determine the cells of origin of a particular set of axons.



(E) In situ hybridization: enkephalin gene expression



(F) Expression of *c-fos* in activated cells



(G) HRP-filled motoneuron

capable of generating their own electrical impulses, they receive synapses directly from neurons and also monitor the activity of nearby neuronal synapses. They then communicate among themselves and with the neighboring neurons to modulate the neurons' responses (Fields and Stevens-Graham, 2002; Mauch et al., 2001; Zonta et al., 2003).

A second type of glial cell is the **microglial cell**. As the name suggests, microglial cells are very small. They are also remarkably active, continually extending and withdrawing very fine processes that, when they contact a site of damage, form a spherical containment zone around the injury (Davalos et al., 2005). Large numbers of microglial cells migrate to sites of injury or disease in the nervous system, apparently to remove debris from injured or dead cells.

The third and fourth types of glial cells—*oligodendrocytes* and *Schwann cells*—perform a very different yet vital function for neurons, as the next section describes.

Some glial cells wrap around axons, forming myelin sheaths

All along the length of the axons of many neurons, adjacent glial cells wrap sections of the axon in sheaths of **myelin**, a fatty insulating substance, giving the axon the appearance of a string of slender beads. The process of ensheathing axons is termed **myelination**. Between each pair of myelinated segments is a small gap where the axonal membrane is exposed, called a **node of Ranvier** (**Figure 2.6*b***). As we will see in Chapter 3, the myelin sheathing and nodes of Ranvier greatly increase the speed at which neural impulses are conducted. So it's not surprising that anything that interferes with the myelin sheath, such as the demyelinating disease **multiple sclerosis**, can have catastrophic consequences for the individual.

Within the brain and spinal cord, the myelin sheath is formed by a type of glial cell called an **oligodendrocyte** (see Figure 2.6*b*). This cell is much smaller than an astrocyte and has fewer extensions (the Greek *oligos* means "few"). A single oligodendrocyte typically contributes sheathing to numerous adjacent axons, and oligodendrocytes are also commonly associated with nerve cell bodies. The regularity of the wrapping is nicely illustrated in cross sections of the axon (see Figure 2.6*b*). The process of myelination continues for a long time in humans—in some brain regions for 10 to 15 years after birth, and possibly throughout life. For axons outside the brain and spinal cord, myelin is provided by another type of glial cell: the **Schwann cell**. A single Schwann cell ensheathes a limited length of a single axon.

Many thin, short axons lack myelin but still are surrounded by oligodendrocytes or Schwann cells, which act to segregate the unmyelinated axons (**Figure 2.6*c***). Furthermore, the manner in which glial cells surround some synaptic contacts suggests that one of their roles is to insulate and isolate synapses to prevent interference (**Figure 2.6*d***).

Glial cells are of clinical interest because they form many of the tumors that arise in the brain. Furthermore, some glial cells, especially astrocytes, respond to brain injury by changing in size—that is, by swelling. This **edema** damages neurons and is responsible for many symptoms of brain injuries.

The neuronal cell body and dendrites receive information across synapses

The arrangement of a neuron's dendrites—its tree branch–like **arborization**—reflects the cell's information-processing function. The surfaces of the dendrites are covered with contacts from other neurons, the synapses. Most neurons receive thousands of synaptic contacts, through which information is transmitted from **presynaptic** neurons to the **postsynaptic** neuron. A synapse typically has three principal components (**Figure 2.7**):

1. The **presynaptic membrane**, on the axon terminal of the presynaptic neuron
2. A specialized **postsynaptic membrane** on the surface of the dendrite or cell body of the postsynaptic neuron
3. A **synaptic cleft**, the gap of about 20 to 40 nanometers (nm) that separates the presynaptic and postsynaptic membranes

Presynaptic axon terminals contain many small spheres, called **synaptic vesicles**, 30 to 140 nm in diameter. Each vesicle contains a specialized chemical substance, or

microglial cells Also called *microglia*. Extremely small glial cells that remove cellular debris from injured or dead cells.

myelin The fatty insulation around an axon, formed by accessory cells, that improves the speed of conduction of nerve impulses.

myelination The process of myelin formation.

node of Ranvier A gap between successive segments of the myelin sheath where the axon membrane is exposed.

multiple sclerosis Literally "many scars"; a disorder characterized by widespread degeneration of myelin.

oligodendrocyte A type of glial cell that is commonly associated with nerve cell bodies.

Schwann cell The accessory cell that forms myelin in the peripheral nervous system.

edema The swelling of tissue, especially in the brain, in response to injury.

arborization The elaborate branching of the dendrites of some neurons.

presynaptic Referring to the region of the synapse that releases neurotransmitter.

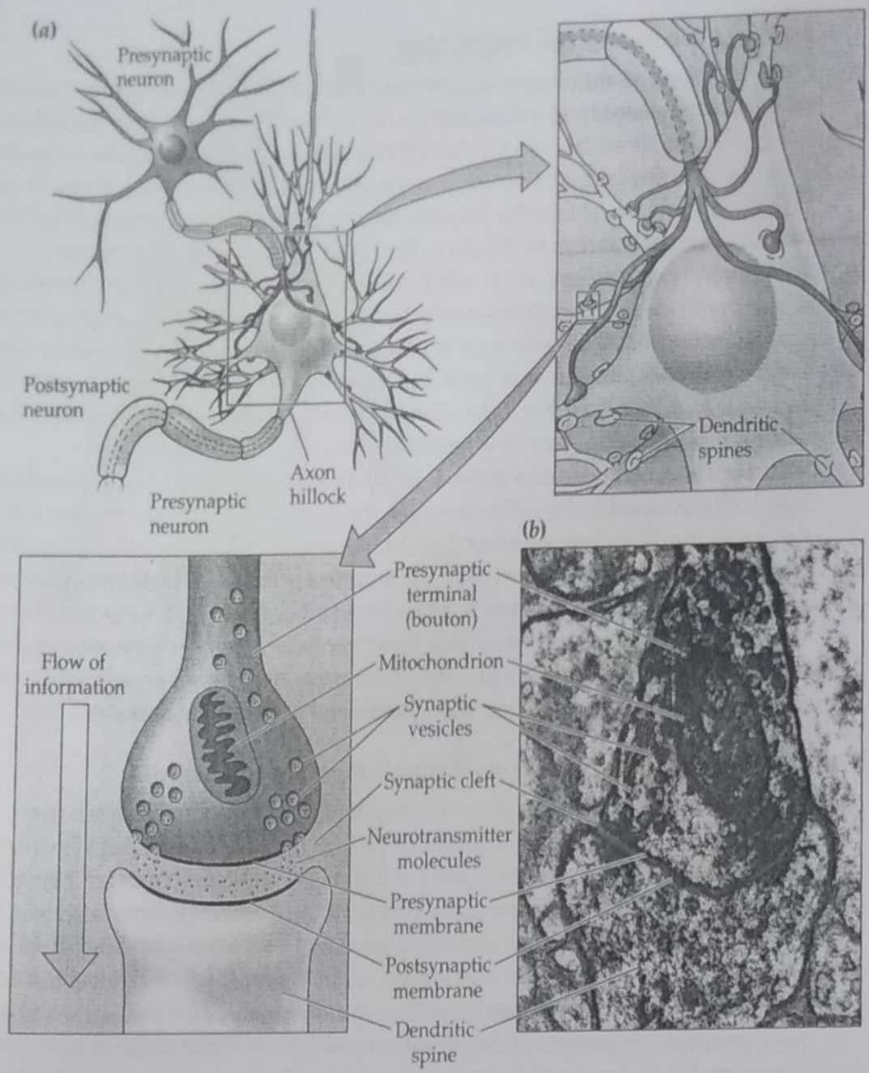
postsynaptic Referring to the region of a synapse that receives and responds to neurotransmitter.

presynaptic membrane The specialized membrane of the axon terminal of the neuron that transmits information by releasing neurotransmitter.

postsynaptic membrane The specialized membrane on the surface of the cell that receives information from a presynaptic neuron.

synaptic cleft The space between the presynaptic and postsynaptic elements.

synaptic vesicle A small, spherical structure that contains molecules of synaptic transmitter.


(a)
Presynaptic neuron
Postsynaptic neuron
Presynaptic neuron
Axon hillock
Dendritic spines
(b)
Flow of information
Presynaptic terminal (bouton)
Mitochondrion
Synaptic vesicles
Synaptic cleft
Neurotransmitter molecules
Presynaptic membrane
Postsynaptic membrane
Dendritic spine

2.7 Synapses (*a*) Axons typically form a synapse on the cell body or dendrites of a neuron. On dendrites, synapses may form on dendritic spines or on the shaft of a dendrite. (*b*) This electron micrograph provides a view of the fine structure of a synapse.

neurotransmitter, that the neuron uses to communicate with postsynaptic neurons. In response to electrical activity in the axon, these vesicles fuse to the presynaptic membrane and release molecules of neurotransmitter into the cleft. After flowing across the cleft, the released neurotransmitter produces electrical changes in the postsynaptic cell that may be either excitatory or inhibitory. Many different substances are known to act as neurotransmitters; we will discuss neurotransmitters in depth in Chapter 4.

The postsynaptic membrane contains a high density of **receptors**, the specialized protein molecules that capture and react to molecules of the neurotransmitter. Because each synapse occupies a very small patch of the postsynaptic neuron—less than $1\ \mu m^2$—a large number of synapses can cover the surfaces of the dendrites and cell body. Some neurons receive as many as 100,000 synaptic contacts, although a more common number is about 5000 to 10,000. As you might expect, neurons with elaborate dendrites tend to have more synaptic inputs.

Studding the dendrites of many neurons are outgrowths called **dendritic spines** (see Figure 2.7), which, by effectively increasing the surface area of the dendrites, allow for extra synaptic contacts. Both the number and structure of dendritic spines may be rapidly altered by experience, such as training or exposure to sensory stimuli (see Chapter 18). This property of dendritic spines, a form of **neural plasticity**, has made them the focus of intensive research efforts. The neuroplastic changes of dendritic spines may range from minute-by-minute fluctuations to lifelong stable changes (Grutzendler et al., 2002; Trachtenberg et al., 2002).

neurotransmitter Also called *synaptic transmitter, chemical transmitter,* or *simply transmitter.* The chemical released from the presynaptic axon terminal, that serves as the basis of communication between neurons.

receptor Also called *receptor molecule.* A protein that captures and reacts to molecules of a transmitter or hormone.

dendritic spine An outgrowth along the dendrite of a neuron.

neural plasticity Also called *neuroplasticity.* The ability of the nervous system to change in response to experience or the environment.

The axon is a specialized output zone

A typical axon has several distinct regions (see Figure 2.5). In multipolar neurons the axon arises from the **axon hillock** ("little hill"), a cone-shaped projection from the cell body (see Figure 2.7*a*). The axon hillock is the neuron's integration zone, giving rise to the electrical impulses that carry the neuron's message along the axon toward its targets (see Chapter 3). The axon beyond the hillock is tubular, with a diameter ranging from 0.5 to 20 μm in mammals and up to 500 μm in the "giant" axons of some invertebrates.

With very few exceptions, nerve cells have only one axon. But axons often divide into several branches, called **axon collaterals**. Because of this branching, a single nerve cell can exert influence over a wide array of other cells. Toward its ending, an axon or a collateral typically divides into numerous fine branches. At the ends of these branches are found the axon terminals that make synaptic contacts on other cells, or **innervate** them. **Table 2.1** compares the main structural features of axons and dendrites.

The cell body manufactures proteins under the guidance of the DNA (deoxyribonucleic acid) contained in the cell nucleus (see the appendix). Therefore, proteins that are needed for the cell to function properly must be transported from the cell body to distant regions in the axon, and recycled materials must be returned to the cell body. The movement of materials within the axon is referred to as **axonal transport**. Some molecules are transported along axons at a "slow" rate (less than 8 mm per day); others are transported by a "fast" system (200–400 mm per day). Some of the details of this process are discussed on the website in **A Step Further: The Cytoskeleton and Axonal Transport**.

Neurons and glial cells form information-processing circuits

Supported and influenced by glial cells, and sharing information across synapses, neurons form ensembles that perform intricate processing of information, and that in many cases are subject to constant remodeling in response to life experiences. In Chapter 3 we will turn to the incredible processes by which the basic units of information—electrical signals—are formed, modified, and transmitted by neurons. For complicated high-level processes, these cell assemblies may involve vast numbers of cells and synaptic contacts, combined together in circuits and structures that are visible to the naked eye as the major anatomical components of the central nervous system. These major divisions are our next topic. In most cases the pattern of connections between neurons changes in form and function in response to life experiences, as we'll see in several later chapters.

The Nervous System Consists of Central and Peripheral Divisions

In this section we'll describe the gross anatomy of the human nervous system—the components of the brain visible to the unaided eye. **Figure 2.8a** presents a view of the entire human nervous system. Examining the nervous system from this viewpoint re-

TABLE 2.1 Distinctions between Axons and Dendrites

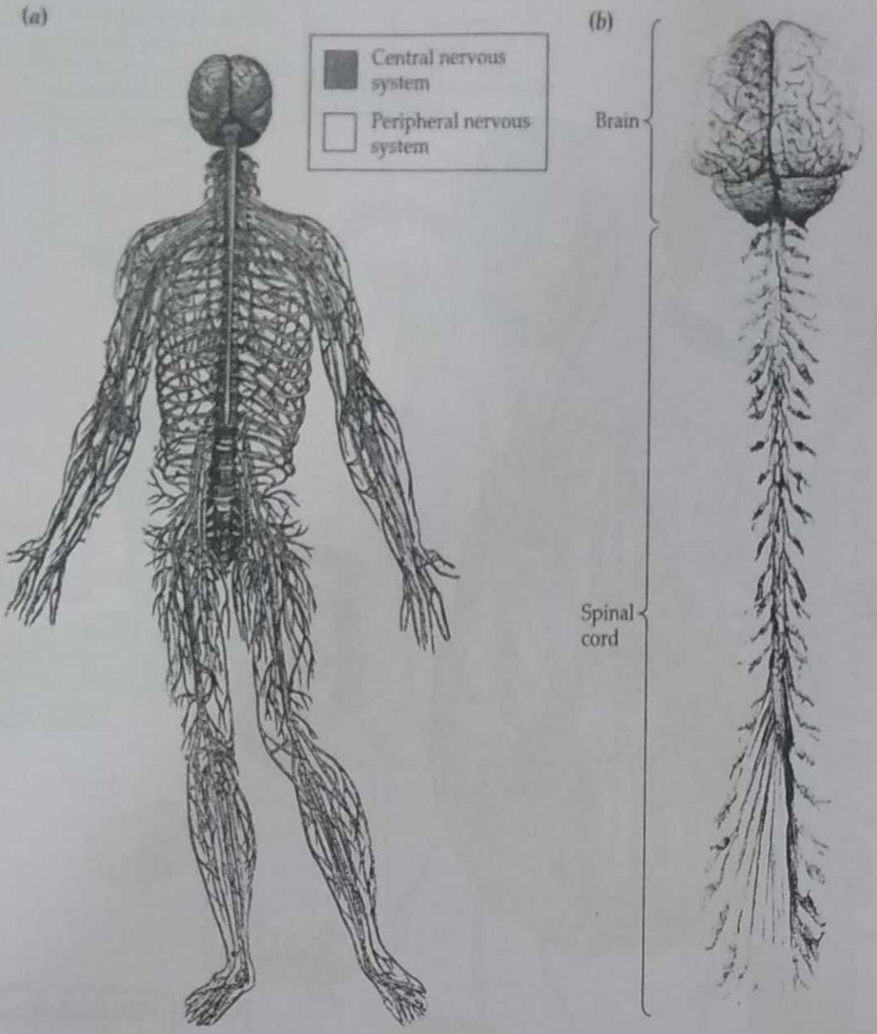
Property	Axons	Dendrites
Number	Usually one per neuron, with many terminal branches	Usually many per neuron
Diameter	Uniform until start of terminal branching	Taper progressively toward ending
Axon hillock	Present	No hillock-like region
Sheathing	Usually covered with myelin	No myelin sheath
Length	Range from practically nonexistent to several meters long	Usually much shorter than axons
Branching	Along length, branches tend to be perpendicular	Along length, branches occur over wide range of acute angles

axon hillock A cone-shaped area from which the axon originates out of the cell body.

axon collateral A branch of an axon from a single neuron.

innervate To provide neural input.

axonal transport The transportation of materials from the neuron cell body to distant regions in the dendrites and axons, and from the axon terminals back to the cell body.



2.8 The Central and Peripheral Nervous Systems (*a*) This view of the nervous system is a composite of two drawings. A modern view of the central nervous system (the brain and spinal cord), shown in blue, is superimposed on a rendering of the peripheral nervous system by the great sixteenth-century anatomist Andreas Vesalius (1514–1564). The peripheral nervous system, shown in yellow, courses through the body and connects all body organs and systems to the central nervous system. (*b*) The brain and spinal cord together form the central nervous system. Note that the solid part of the spinal cord terminates in the middle of the lower back. Below this point a spray of fibers called the *cauda equina* (Latin for "horse's tail") continues downward inside the spinal column.

veals a natural subdivision into a **peripheral nervous system** (all nervous system parts that are outside the bony skull and spinal column) and a **central nervous system** (**CNS**), consisting of the brain and spinal cord (**Figure 2.8*b***).

The peripheral nervous system has three components

The peripheral nervous system consists of **nerves**—collections of axons bundled together—that extend throughout the body. These nerves transmit information to muscles (in motor pathways) or arise from sensory surfaces (in sensory pathways). Three components make up the peripheral nervous system: (1) the **cranial nerves**, which are connected directly to the brain; (2) the **spinal nerves**, which are connected at regular intervals to the spinal cord; and (3) the **autonomic nervous system**, a regulatory system that primarily controls the viscera (internal organs). All three components communicate sensory information to the CNS and transmit commands from the CNS to the body.

THE CRANIAL NERVES The 12 pairs of cranial nerves serve chiefly the sensory and motor systems of the head (**Figure 2.9**). These nerves pass through small openings in the skull to enter or leave the brain. The cranial nerves are known both by name and by Roman numeral. Three cranial nerves are exclusively sensory pathways to the brain: the olfactory (I), optic (II), and vestibulocochlear (VIII) nerves. Five are exclusively motor pathways from the brain: the oculomotor (III), trochlear (IV), and abducens (VI) nerves innervate muscles to move the eye; the spinal accessory (XI) nerves control neck muscles; and the hypoglossal (XII) nerves control the tongue.

The remaining cranial nerves have both sensory and motor functions. The trigeminal (V), for example, serves facial sensation through some axons, and it controls chew-

peripheral nervous system The portion of the nervous system that includes all the nerves and neurons outside the brain and spinal cord.

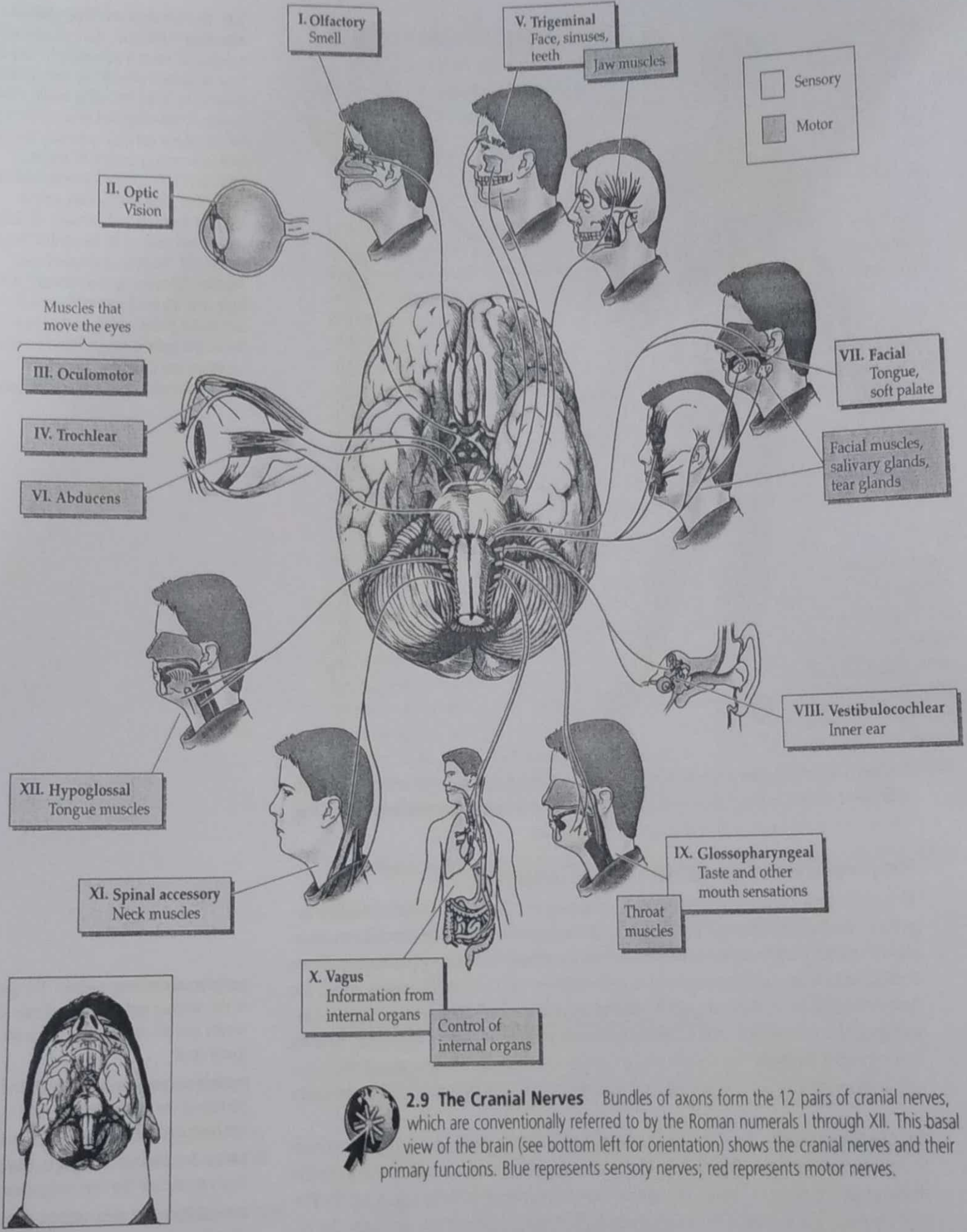
central nervous system (CNS) The portion of the nervous system that includes the brain and the spinal cord.

nerve A collection of axons bundled together outside the central nervous system.

cranial nerve A nerve that is connected directly to the brain.

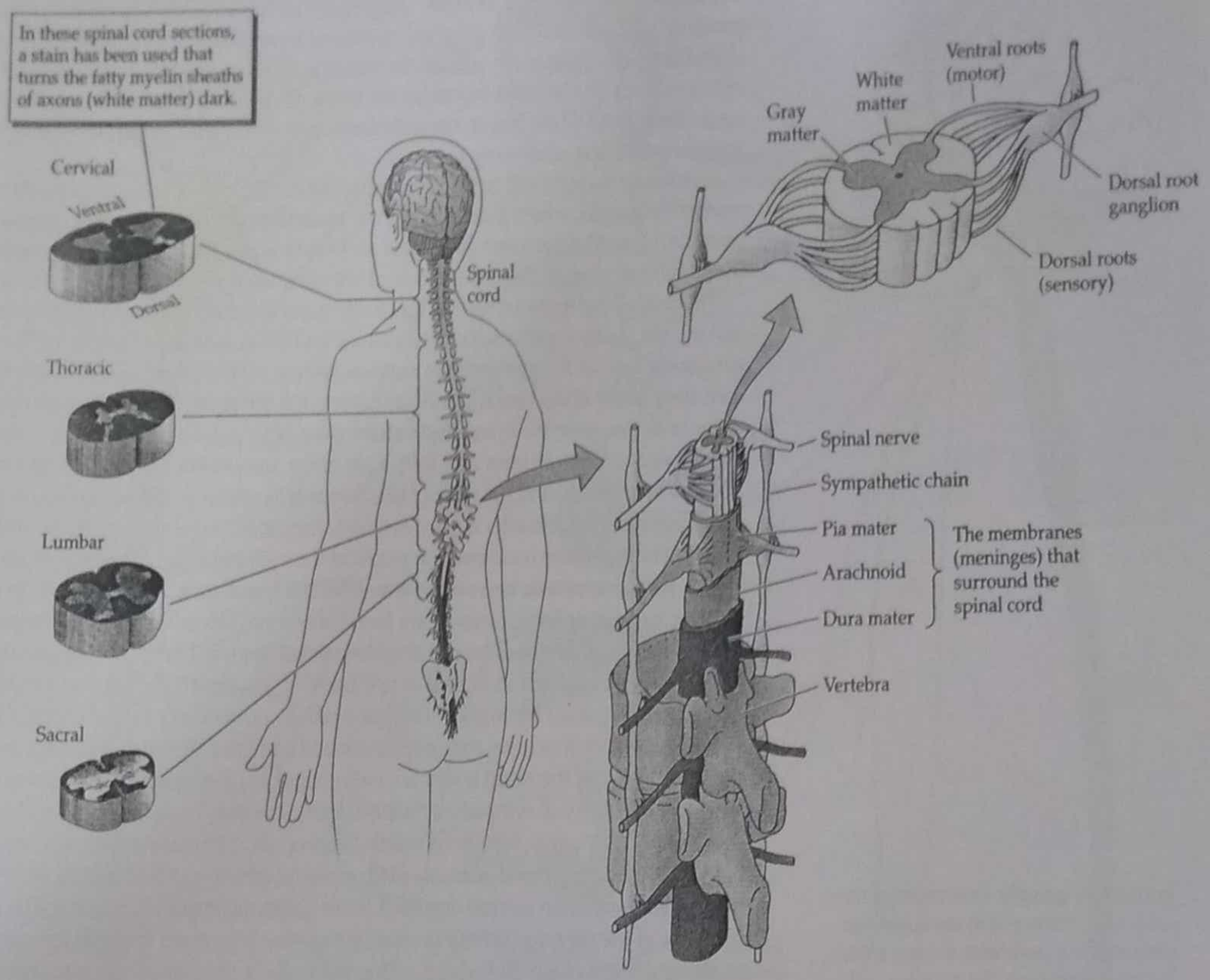
spinal nerve Also called *somatic nerve*. A nerve that emerges from the spinal cord.

autonomic nervous system The part of the peripheral nervous system that supplies neural connections to glands and to smooth muscles of internal organs.


I. Olfactory
Smell
V. Trigeminal
Face, sinuses, teeth
Jaw muscles
Sensory
Motor
II. Optic
Vision
Muscles that move the eyes
III. Oculomotor
IV. Trochlear
VI. Abducens
VII. Facial
Tongue, soft palate
Facial muscles, salivary glands, tear glands
VIII. Vestibulocochlear
Inner ear
XII. Hypoglossal
Tongue muscles
XI. Spinal accessory
Neck muscles
IX. Glossopharyngeal
Taste and other mouth sensations
Throat muscles
X. Vagus
Information from internal organs
Control of internal organs

2.9 The Cranial Nerves Bundles of axons form the 12 pairs of cranial nerves, which are conventionally referred to by the Roman numerals I through XII. This basal view of the brain (see bottom left for orientation) shows the cranial nerves and their primary functions. Blue represents sensory nerves; red represents motor nerves.

ing movements through other axons. The facial (VII) nerves control facial muscles and receive taste sensation, and the glossopharyngeal (IX) nerves receive sensation from the throat and control the muscles there. The vagus (X) nerve extends far from the head, running to the heart, liver, and intestines. Its long, convoluted route is the reason for its name, which is Latin for "wandering."



In these spinal cord sections, a stain has been used that turns the fatty myelin sheaths of axons (white matter) dark.

2.10 The Spinal Cord and Spinal Nerves (*Middle*) The spinal column runs from the base of the brain to the coccyx (tailbone); a pair of nerves emerges from each level (see Figure 2.8*b*). (*Bottom right*) The spinal cord is surrounded by bony vertebrae and is enclosed in three membrane layers (the meninges). Each vertebra has an opening on each side through which the spinal nerves pass. (*Top right*) The spinal cord gray matter is located in the center of the cord and is surrounded by white matter. In the gray matter are interneurons and the motoneurons that send axons to the muscles. The white matter consists of myelinated axons that run up and down the spinal column. (*Left*) These stained cross sections show the spinal cord at the cervical, thoracic, lumbar, and sacral levels. (Photographs from Hanaway et al., 1998.)

THE SPINAL NERVES Along the length of the spinal cord are 31 pairs of spinal nerves (also called *somatic nerves*), with one member of each pair for each side of the body (**Figure 2.10**). These nerves join the spinal cord at regularly spaced intervals through openings in the backbone. Each spinal nerve consists of the fusion of two distinct branches, called *roots*, which are functionally different. The **dorsal** (back) **root** of each spinal nerve consists of sensory projections from the body to the spinal cord. The **ventral** (front) **root** consists of motor projections from the spinal cord to the muscles.

The name of a spinal nerve is the same as the segment of spinal cord to which it is connected: there are 8 **cervical** (neck), 12 **thoracic** (trunk), 5 **lumbar** (lower back), 5 **sacral** (pelvic), and 1 **coccygeal** (bottom) spinal segments. We refer to the spinal nerve that is connected to the twelfth segment of the thoracic portion of the spinal cord as *T12*, the nerve connected to the third segment of the sacral portion as *S3*, and so on. Fibers from different spinal nerves join to form peripheral nerves, usually at some distance from the spinal cord.

dorsal root The branch of a spinal nerve, entering the dorsal horn of the spinal cord, that carries sensory information from the peripheral nervous system to the spinal cord.

ventral root The branch of a spinal nerve, arising from the ventral horn of the spinal cord, that carries motor messages from the spinal cord to the peripheral nervous system.

cervical Referring to the topmost 8 segments of the spinal cord, in the neck region.

thoracic Referring to the 12 spinal segments below the cervical (neck) portion of the spinal cord, corresponding to the chest.

lumbar Referring to the 5 spinal segments that make up the upper part of the lower back.

sacral Referring to the 5 spinal segments that make up the lower part of the lower back.

coccygeal Referring to the lowest spinal vertebra (also known as the tailbone).

THE AUTONOMIC NERVOUS SYSTEM Aggregates of neurons called **autonomic** ("independent") **ganglia** (singular *ganglion*), are found in various locations in the body, outside of the CNS. Their name reflects the historical belief that these neural structures act independently of the brain, but today we know otherwise: the autonomic ganglia are controlled by the CNS. In fact, the autonomic nervous system spans both the central and the peripheral nervous systems.

Autonomic neurons within the brain and spinal cord send their axons to innervate neurons in the ganglia, which in turn send their axons to innervate all the major organs. The central neurons that innervate the ganglia are known as **preganglionic** autonomic neurons; the ganglionic neurons that innervate the body are known as **postganglionic** neurons.

The autonomic nervous system has three major divisions: the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system. The preganglionic cells of the **sympathetic nervous system** are found exclusively in the spinal cord, specifically in the thoracic and lumbar regions. These cells send their axons a short distance to innervate the **sympathetic chain**, autonomic ganglia running along each side of the spinal column (**Figure 2.11** *left*). Cells of the sympathetic chain innervate smooth muscles in organs and in the walls of blood vessels. A convenient, if somewhat oversimplified, summary of the effects of sympathetic activation is that it prepares the body for action: blood pressure increases, the pupils of the eyes widen, and the heart quickens.

The **parasympathetic nervous system** (from the Greek *para*, "around") gets its name because its preganglionic neurons are found above and below those of the sympathetic system—in the brain and the sacral spinal cord (**Figure 2.11** ***right***). Parasympathetic ganglia are not collected in a chain as sympathetic ganglia are. Rather, parasympathetic ganglia are dispersed throughout the body, usually positioned near the organ affected.

For many body functions, the sympathetic and parasympathetic divisions act in opposite directions, and the result is very accurate control. For example, the heartbeat is quickened by the activity of sympathetic nerves during exercise, but it is slowed by the vagus nerve (part of the parasympathetic system) during rest. Sympathetic activation constricts blood vessels, raising blood pressure, while parasympathetic activation relaxes vessel walls; sympathetic activation inhibits digestion, while parasympathetic stimulates it. The simplified view of the parasympathetic division is thus that it prepares the body for rest.

Resembling a mesh embedded within the walls of the digestive organs, the **enteric nervous system** is a local network of sensory and motor neurons that regulates the functioning of the gut. It is innervated by both sympathetic and parasympathetic neurons, and thus it is ordinarily under the control of the CNS. Because it regulates digestive activities of the gut, the enteric nervous system plays a key role in maintaining fluid and nutrient balances in the body (discussed in Chapter 13).

The sympathetic, parasympathetic, and enteric nervous systems are "autonomous" also in another sense: their functions are not subject to conscious "voluntary" control in the same way that we can control our movements.

The central nervous system consists of the brain and spinal cord

The spinal cord funnels sensory information from the body up to the brain and conveys brain motor commands out to the body. The spinal cord also contains circuits that perform local processing and control simple units of behavior, such as reflexes. We will discuss the anatomy of the spinal cord later, when we're examining sensation (in Chapter 8) and movement (in Chapter 11). For now we will limit our focus to the executive portion of the CNS: the brain.

BRAIN FEATURES THAT ARE VISIBLE TO THE NAKED EYE Given the importance of the adult human brain, it is surprising that, on average, it weighs a mere 1400 g, just 2% of the average body weight. However, even casual inspection reveals that what the brain lacks in weight it makes up for in intricacy. **Figure 2.12** offers three views of the human brain in standard orientations. These views will be helpful in our future discussions. Viewed from the side (see Figure 2.12*a*) or from the top, the human brain is dominated by the large **cerebral hemispheres**.

autonomic ganglia Collections of nerve cell bodies, belonging to the autonomic division of the peripheral nervous system, that are found in various locations and innervate the major organs.

preganglionic "Before the ganglion." Referring to neurons in the autonomic nervous system that run from the central nervous system to the autonomic ganglia.

postganglionic "After the ganglion." Referring to neurons in the autonomic nervous system that run from the autonomic ganglia to various targets in the body.

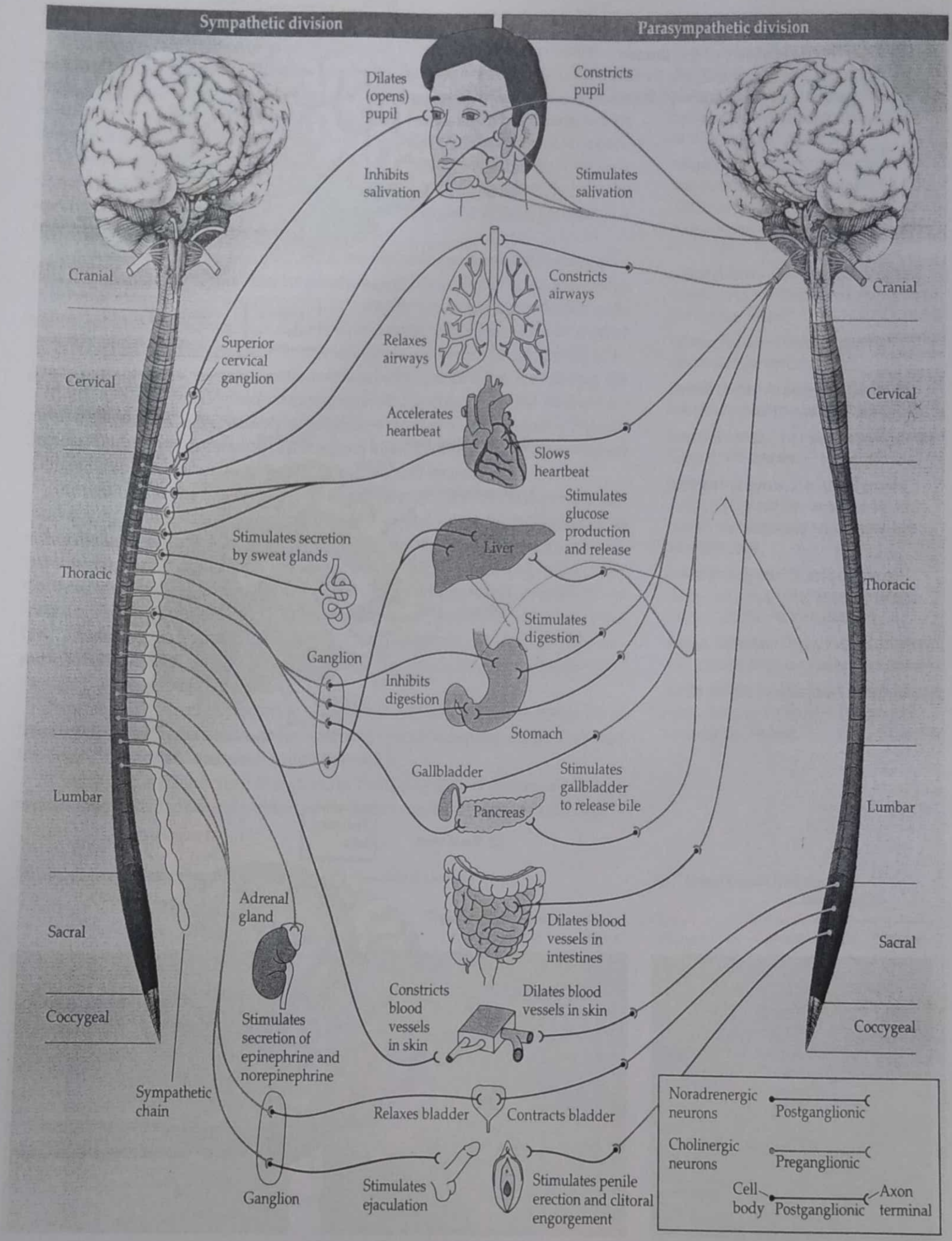
sympathetic nervous system One of two systems that compose the autonomic nervous system. Arises from the thoracic and lumbar spinal cord.

sympathetic chain A chain of ganglia that runs along each side of the spinal column; part of the sympathetic nervous system.

parasympathetic nervous system One of two systems that compose the autonomic nervous system. Arises from both the cranial nerves and the sacral spinal cord.

enteric nervous system An extensive meshlike system of neurons that governs the functioning of the gut.

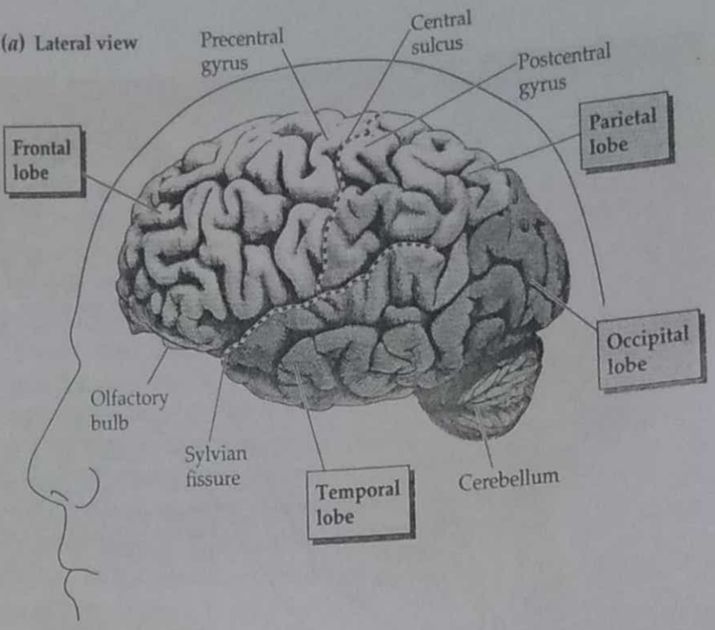
cerebral hemispheres The right and left halves of the forebrain.


Sympathetic division
Parasympathetic division
Dilates (opens) pupil
Constricts pupil
Inhibits salivation
Stimulates salivation
Cranial
Constricts airways
Relaxes airways
Superior cervical ganglion
Cervical
Accelerates heartbeat
Slows heartbeat
Stimulates glucose production and release
Liver
Stimulates secretion by sweat glands
Thoracic
Stimulates digestion
Ganglion
Inhibits digestion
Stomach
Gallbladder
Stimulates gallbladder to release bile
Pancreas
Lumbar
Adrenal gland
Dilates blood vessels in intestines
Sacral
Constricts blood vessels in skin
Dilates blood vessels in skin
Coccygeal
Stimulates secretion of epinephrine and norepinephrine
Sympathetic chain
Relaxes bladder
Contracts bladder
Ganglion
Stimulates ejaculation
Stimulates penile erection and clitoral engorgement
Noradrenergic neurons
Postganglionic
Cholinergic neurons
Preganglionic
Cell body
Postganglionic
Axon terminal

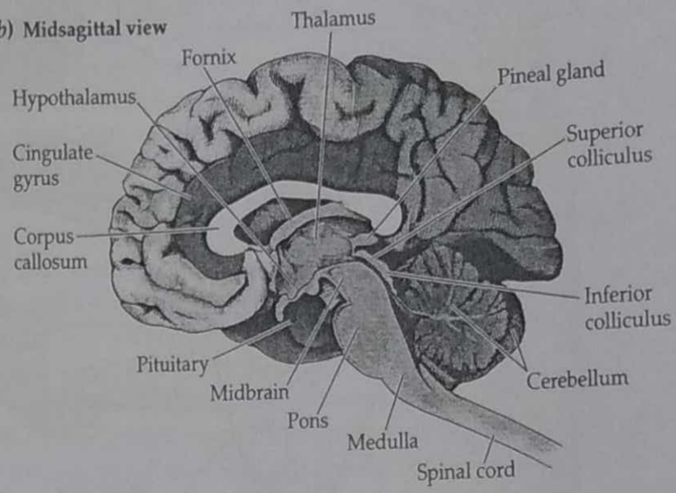
2.11 The Autonomic Nervous System (*Left*) The sympathetic division of the autonomic nervous system consists of the sympathetic chains and the nerve fibers that flow from them. (*Right*) The parasympathetic division arises from both the cranial and the sacral parts of the spinal cord. All preganglionic axons, whether sympathetic or parasympathetic, release acetylcholine (from which we get the adjective *cholinergic*) as a neurotransmitter, as do parasympathetic postganglionic cells. Sympathetic postganglionic cells use norepinephrine (also known as noradrenaline; hence *noradrenergic*) as a neurotransmitter. The two different postganglionic transmitters are what allow the autonomic nervous system to have two opposing effects on target organs. Neurotransmitters are discussed in detail in Chapter 4.

2.12 Three Views of the Human Brain (a) Lateral view (from the side). (b) Midsagittal (midline) view. (c) Basal view (from below).

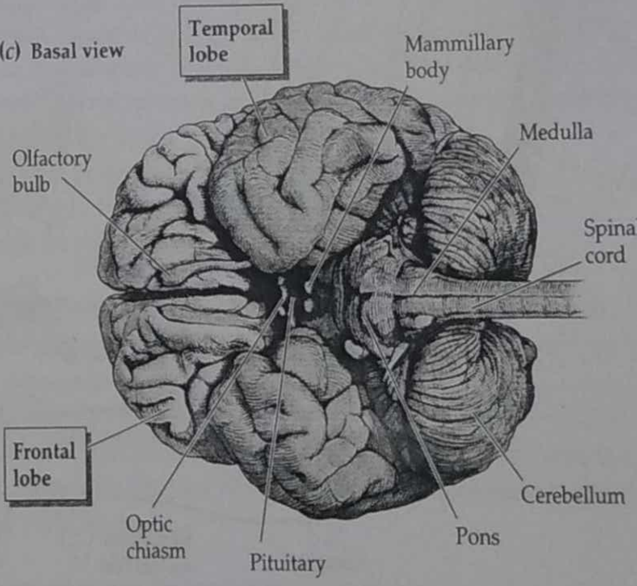
(*a*) **Lateral view**


Precentral gyrus
Central sulcus
Postcentral gyrus
Frontal lobe
Parietal lobe
Occipital lobe
Olfactory bulb
Sylvian fissure
Temporal lobe
Cerebellum

(*b*) **Midsagittal view**


Thalamus
Fornix
Hypothalamus
Pineal gland
Superior colliculus
Cingulate gyrus
Corpus callosum
Inferior colliculus
Pituitary
Midbrain
Pons
Medulla
Spinal cord
Cerebellum

(*c*) **Basal view**


Temporal lobe
Mammillary body
Medulla
Olfactory bulb
Spinal cord
Frontal lobe
Cerebellum
Optic chiasm
Pituitary
Pons

The convolutions of the paired cerebral hemispheres are the result of elaborate folding together of tissue. The resulting ridges of tissue, called **gyri** (singular *gyrus*), are separated from each other by furrows called **sulci** (singular *sulcus*). Such folding enormously increases the cerebral surface area; about two-thirds of the cerebral surface is hidden in the depths of these folds.

gyrus A ridged or raised portion of a convoluted brain surface.

sulcus A furrow of a convoluted brain surface.

The major sectors of the cerebral hemispheres are the **frontal**, **parietal**, **temporal**, and **occipital** regions, or **lobes**. These lobes, named after the bones of the skull that overlie them, are distinguished by colors in Figure 2.12. In some cases, the boundaries between adjacent lobes are very clear; for example, the lateral sulcus, or **Sylvian fissure** (which demarcates the temporal lobe), and the **central sulcus** (which divides frontal from parietal lobes) are quite distinct. The boundaries dividing the occipital lobes from the parietal and temporal lobes are less well defined. The outer shell of the hemispheres is the **cerebral cortex**, sometimes referred to as simply the *cortex* (which, Latin for "bark of a tree," refers to the outermost layers of a structure).

In general, the cortex may be regarded as the seat of complex cognition; damage to the cortex may impair "higher" functions such as speech, memory, or visual processing. In contrast, "lower" parts of the brain regulate respiration, heart rate, and other basic functions. Note that the four lobes of the brain normally collaborate with one another to serve myriad different processes. In a general sense, however, we can identify categories of processing that are particularly associated with specific lobes. For example, the occipital lobes receive and process information from the eyes, giving rise to many aspects of the sense of vision. Auditory information is directed to the temporal lobes, and damage there can impair hearing (the temporal lobes are also particularly associated with the sense of smell, and with aspects of learning and memory).

The sense of touch is mediated by a strip of parietal cortex just behind the central sulcus called the **postcentral gyrus**, and in front of the central sulcus, the **precentral gyrus** of the frontal lobe is crucial for motor control. In fact, Wilder Penfield's experiments with stimulation mapping of the brain, which we discussed at the beginning of the chapter, revealed that the precentral gyrus contains an orderly map of the muscles of the body (see Figure 11.12). Similarly, the postcentral gyrus contains a sensory map of the body (Penfield and Rasmussen, 1950). A large, C-shaped bundle of axons called the **corpus callosum** (see Figure 2.12*b*) crosses the midline and allows communication between the right and left cerebral hemispheres.

To get the most out of our discussion of these systems, you will need to understand the conventions that anatomists use for describing various viewpoints of the body and the brain. These conventions are described in **Box 2.2**.

No matter what plane is used to section the brain, two distinct shades of color are evident (**Figure 2.13**). The light-colored **white matter** consists mostly of fiber tracts. It

frontal lobe The most anterior portion of the cerebral cortex.

parietal lobes Large regions of cortex lying between the frontal and occipital lobes of each cerebral hemisphere.

temporal lobes Large lateral cortical regions of each cerebral hemisphere, continuous with the parietal lobes posteriorly, and separated from the frontal lobe by the Sylvian fissure.

occipital lobes Large regions of cortex covering much of the posterior part of each cerebral hemisphere.

Sylvian fissure A deep fissure that demarcates the temporal lobe.

central sulcus A fissure that divides the frontal lobe from the parietal lobe.

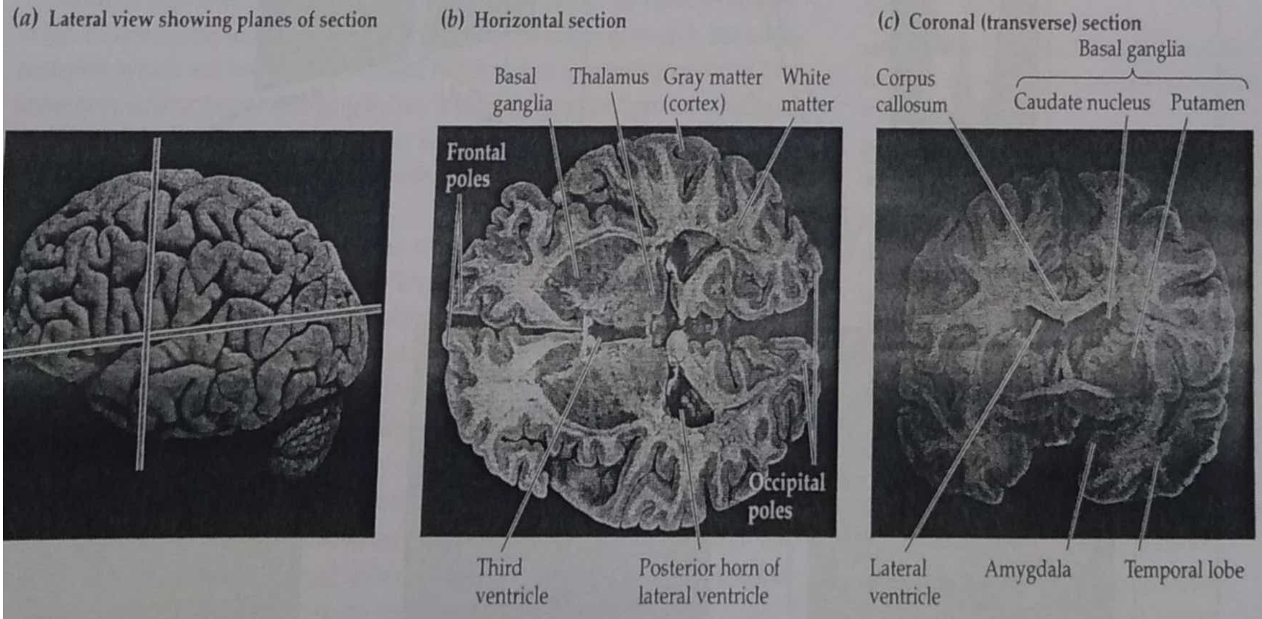
cerebral cortex The outer covering of the cerebral hemispheres.

postcentral gyrus The strip of parietal cortex, just behind the central sulcus, that receives somatosensory information from the entire body.

precentral gyrus The strip of frontal cortex, just in front of the central sulcus, that is crucial for motor control.

corpus callosum The main band of axons that connects the two cerebral hemispheres.

white matter A shiny layer underneath the cortex that consists largely of axons with white myelin sheaths.



3 Inside the Brain (*a*) The colored lines here indicate the planes of section shown in (*b*) and The light color of the white matter is from the fatty myelin surrounding the axons in the major fiber ts. Gray matter consists of cell bodies that form the outer layers of the brain and nuclei within the n. (Photographs courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)

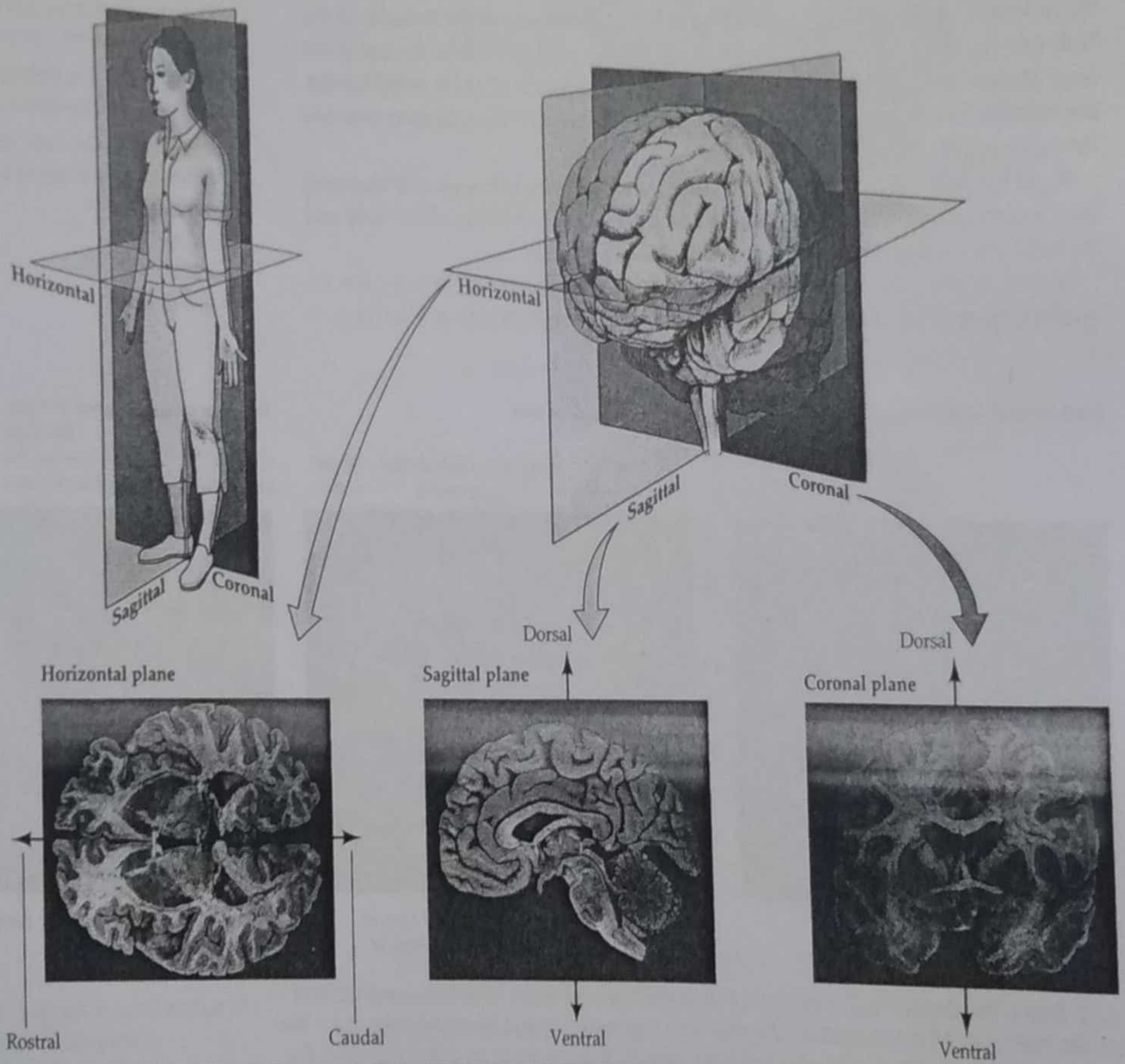
BOX 2.2 Three Customary Orientations for Viewing the Brain and Body

Because the nervous system is a three-dimensional structure, two-dimensional illustrations and diagrams cannot represent it completely. The brain is usually cut in one of three main planes to obtain a two-dimensional section from this three-dimensional object. It is useful to know the terminology and conventions that apply to these sections, which are shown in the figure.

The plane that bisects the body into right and left halves is called the **sagittal plane** (from the Latin *sagitta*, "arrow"). The plane that divides the body into a front (anterior) and a back (posterior) part is called by several names: **coronal plane** (from the Latin *corona*, "crown"), *frontal plane*, or *transverse plane*. For clarity, we will view coronal sections from behind so that the right side of the figure represents the right side of the brain. (In medicine, coronal sections are viewed as if you were facing the patient, with the patient's left on your right.) The third main plane, which divides the brain into upper and lower parts, is called the **horizontal plane**.

In addition, several directional terms are used. **Medial** means "toward the middle" and is contrasted with **lateral**, "toward the side." Relative to one location, a second location is **ipsilateral** if it is on the same side of the body and **contralateral** if on the opposite side of the body. The head end is referred to as **anterior** or **rostral** (from the Latin *rostrum*, "prow of a ship"). The tail end is called **posterior** or **caudal** (from the Latin *cauda*, "tail"). **Proximal** (from the Latin *proximus*, "nearest") means "near the trunk or center," and **distal** means "toward the periphery" or "toward the end of a limb" (distant from the origin or point of attachment).

Dorsal means "toward or at the back," and **ventral** means "toward or at the belly or front." In four-legged animals, such as the cat or the rat, *dorsal* refers to both the back of the body and the top of the head and brain. For consistency in comparing brains among species, this term is also used to refer to the top of the brain of a human or of a



BOX 2.2 (continued)

chimpanzee, even though in such two-legged animals the top of the brain is not at the back of the body. Similarly, *ventral* is understood to designate the bottom of the brain of a two-legged as well as of a four-legged animal.

An additional pair of words is important for describing the flow of information through the nervous system. We call an axon, tract, or nerve **afferent** if it carries information into a region that we are interested in, and **efferent** if it carries information away from the region of interest (a handy way to remember this is that *e*fferents *e*xit but *a*fferents *a*rrive, relative to the region of interest).

Although these terms may seem strange at first, they provide a means of describing anatomy without ambiguity. If you want to become adept with these terms, you might find it helpful to get together with a friend and quiz each other about anatomical relations. "Where's the navel? In a medial position on the ventral surface, caudal to the rib cage, and rostral to the pelvis." (Photographs courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)

gains its appearance from the whitish fatty myelin that ensheathes and insulates the axons of many neurons. The darker-colored **gray matter** is dominated more by nerve cell bodies and dendrites, which are devoid of myelin.

DEVELOPMENTAL SUBDIVISIONS OF THE BRAIN It can be difficult to understand some of the anatomical distinctions applied to the adult human brain. For example, why is the part of the brain closest to the back of head identified as part of the *fore*brain? The key to understanding this confusing terminology is to consider how the brain develops early in life.

In a very young embryo of any vertebrate, the CNS looks like a tube. The walls of this **neural tube** are made of cells, and the interior is filled with fluid. A few weeks after conception, the human neural tube begins to show three separate swellings at the head end (**Figure 2.14*a***): the **forebrain** (or *prosencephalon*), the **midbrain** (or *mesencephalon*), and the **hindbrain** (or *rhombencephalon*). (The term *encephalon*, meaning "brain," comes from the Greek *en*, "in," and *kephale*, "head.")

About 50 days after conception, the forebrain and hindbrain have already developed clear subdivisions. At the very front of the developing brain is the **telencephalon**, which will become the cerebral hemispheres (consisting of cortex plus some deeper structures belonging to two functionally related groups: the basal ganglia and the limbic system). The other part of the forebrain is the **diencephalon** (or "between brain"), which will include regions called the *thalamus* and the *hypothalamus*.

The midbrain (mesencephalon) comes next. Behind it the hindbrain has two divisions: the **metencephalon**, which will develop into the **cerebellum** ("little brain") and the **pons** ("bridge"); and the **myelencephalon**, more commonly called the **medulla**. The term **brainstem** usually refers to the midbrain, pons, and medulla combined. **Figure 2.14*c*** shows the positions of these structures and their relative sizes in the adult human brain. Even when the brain achieves its adult form, it is still a fluid-filled tube, but a tube of very complicated shape.

Each of the five main sections (telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon) can be subdivided in turn. We can work our way from the largest, most general divisions of the nervous system on the left of the schematic in **Figure 2.14*b*** to more-specific ones on the right.

Within each region are aggregations of neurons called **nuclei** (singular *nucleus*) and bundles of axons called **tracts**. Recall that in the periphery, aggregations of neurons are called *ganglia*, and bundles of axons are called *nerves*. Unfortunately, the

gray matter Areas of the brain that are dominated by cell bodies and are devoid of myelin.

neural tube An embryonic structure with subdivisions that correspond to the future forebrain, midbrain, and hindbrain.

forebrain Also called *prosencephalon*. The frontal division of the neural tube, containing the cerebral hemispheres, the thalamus, and the hypothalamus.

midbrain Also called *mesencephalon*. The middle division of the brain.

hindbrain Also called *rhombencephalon*. The rear division of the brain, which, in the mature vertebrate, contains the cerebellum, pons, and medulla.

telencephalon The frontal subdivision of the forebrain that includes the cerebral hemispheres when fully developed.

diencephalon The posterior part of the forebrain, including the thalamus and hypothalamus.

metencephalon A subdivision of the hindbrain that includes the cerebellum and the pons.

cerebellum A structure located at the back of the brain, dorsal to the pons, that is involved in the central regulation of movement.

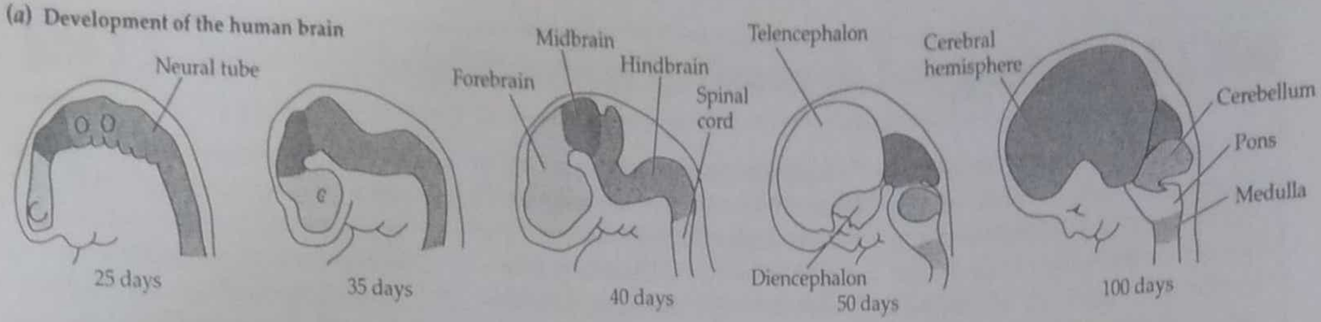
pons A portion of the metencephalon.

myelencephalon or medulla The caudal part of the hindbrain.

brainstem The region of the brain that consists of the midbrain, the pons, and the medulla.

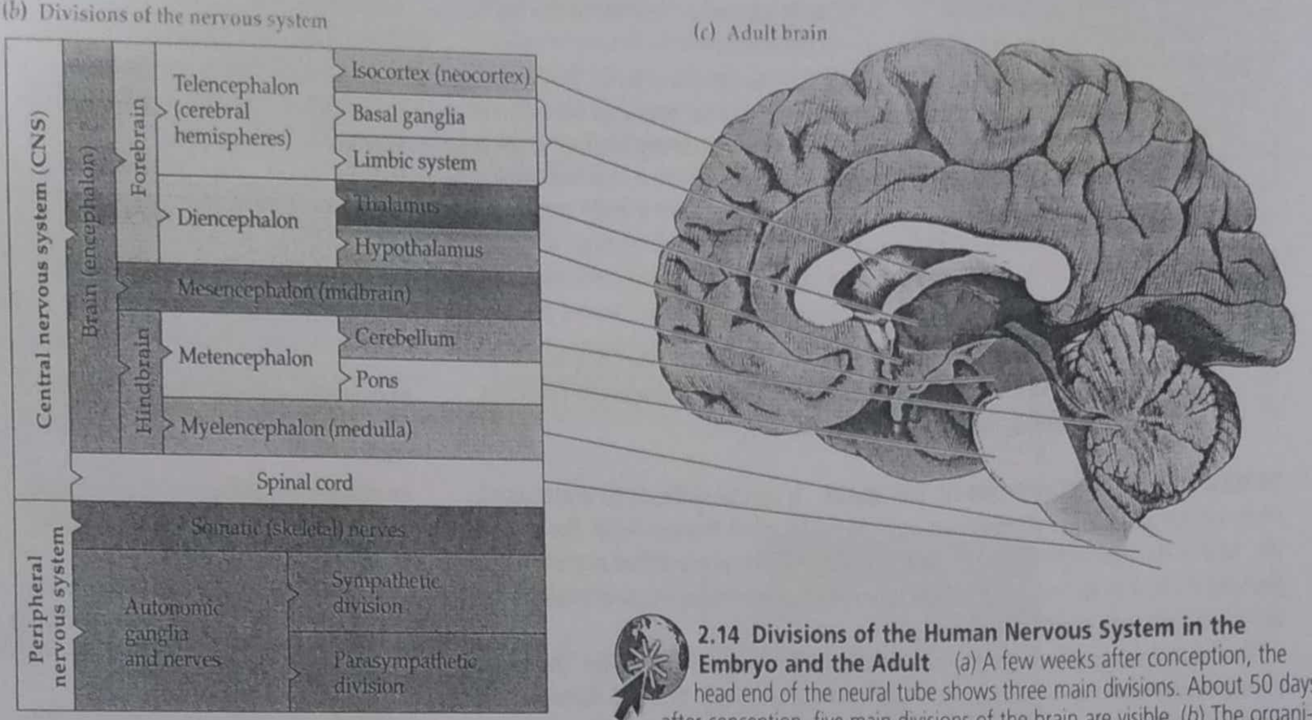
nucleus Here, an anatomical collection of neurons within the central nervous system (e.g., the caudate nucleus).

tract A bundle of axons found within the central nervous system.



(a) Development of the human brain

Neural tube
25 days
35 days
Forebrain
Midbrain
Hindbrain
Spinal cord
40 days
Telencephalon
Diencephalon
50 days
Cerebral hemisphere
Cerebellum
Pons
Medulla
100 days



(b) Divisions of the nervous system

(c) Adult brain

Central nervous system (CNS)
Brain (encephalon)
Forebrain
Telencephalon (cerebral hemispheres)
Isocortex (neocortex)
Basal ganglia
Limbic system
Diencephalon
Thalamus
Hypothalamus
Mesencephalon (midbrain)
Hindbrain
Metencephalon
Cerebellum
Pons
Myelencephalon (medulla)
Spinal cord
Peripheral nervous system
Somatic (skeletal) nerves
Autonomic ganglia and nerves
Sympathetic division
Parasympathetic division

2.14 Divisions of the Human Nervous System in the Embryo and the Adult (a) A few weeks after conception, the head end of the neural tube shows three main divisions. About 50 days after conception, five main divisions of the brain are visible. (b) The organization of these divisions schematically; (c) their positions in the adult brain.

same word *nucleus* can mean either "a collection of nerve cell bodies" or "the spherical center of a single cell," so you must rely on the context to understand which meaning is intended. Because these nuclei and tracts are the same from individual to individual, and often from species to species, they have names too.

You are probably more interested in the functions of all these parts of the brain than in their names, but as we noted earlier, each region serves more than one function, and our knowledge of the functional organization of the brain is subject to constant revision as new findings are reported. With that caveat in mind, let's briefly survey functions of specific brain structures, leaving the detailed discussion for later chapters.

The Brain Is Described by Both Structure and Function

Although there are some single structures around the midline—such as the corpus callosum, pineal gland, and pituitary gland (see Figure 2.12*b*)—most structures are found in both the right and the left sides of the brain. One important principle of the brain in all vertebrates is that the right side of the brain controls the left side of the body, while the left brain controls the right side of the body. In turn, sensory information from the left side of the body goes to the right side of the brain, and so on. So we say that each side of the brain controls the opposite (or *contralateral*; see Box 2.2) side of the body, and we'll see very few exceptions to that rule in coming chapters. We'll learn about how the two cerebral hemispheres interact in Chapter 19, but for now let's review the various components of the brain and their functions.

Within the cerebral hemispheres are the basal ganglia and the limbic system

The **basal ganglia** include the **caudate nucleus**, the **putamen**, and the **globus pallidus** in the telencephalon under the cerebral cortex, and the **substantia nigra** in the midbrain (**Figure 2.15*a***; see also Figure 2.13*b* and *c*). These four nuclei (not really ganglia, despite the unfortunate name *basal ganglia*) are reciprocally connected among themselves and with the cerebral cortex, forming a looping neural system. The basal ganglia are very important in motor control, as we will see in Chapter 11.

The **limbic system** is a loosely defined, widespread network of structures (**Figure 2.15*b***) that are involved in emotion and learning. The **amygdala** (Latin for "almond," because it has that shape) consists of several subdivisions with quite diverse functions, including emotional regulation (Chapter 15) and the perception of odor (Chapter 9). The **hippocampus** (from the Greek *hippokampos*, "sea horse," which it resembles in shape) and the **fornix** are important for learning (Chapter 17). Other components of the limbic system include a strip of cortex in each hemisphere called the **cingulate gyrus**, which is implicated in diverse functions including the direction of attention, and the **olfactory bulb**, which is involved in the sense of smell.

basal ganglia A group of forebrain nuclei (caudate nucleus, globus pallidus, and putamen) found deep within the cerebral hemispheres.

caudate nucleus One of the basal ganglia; it has a long extension or tail.

putamen One of the basal ganglia.

globus pallidus One of the basal ganglia.

substantia nigra A brainstem structure in humans that is related to the basal ganglia and named for its dark pigmentation.

limbic system A loosely defined, widespread group of brain nuclei that innervate each other to form a network.

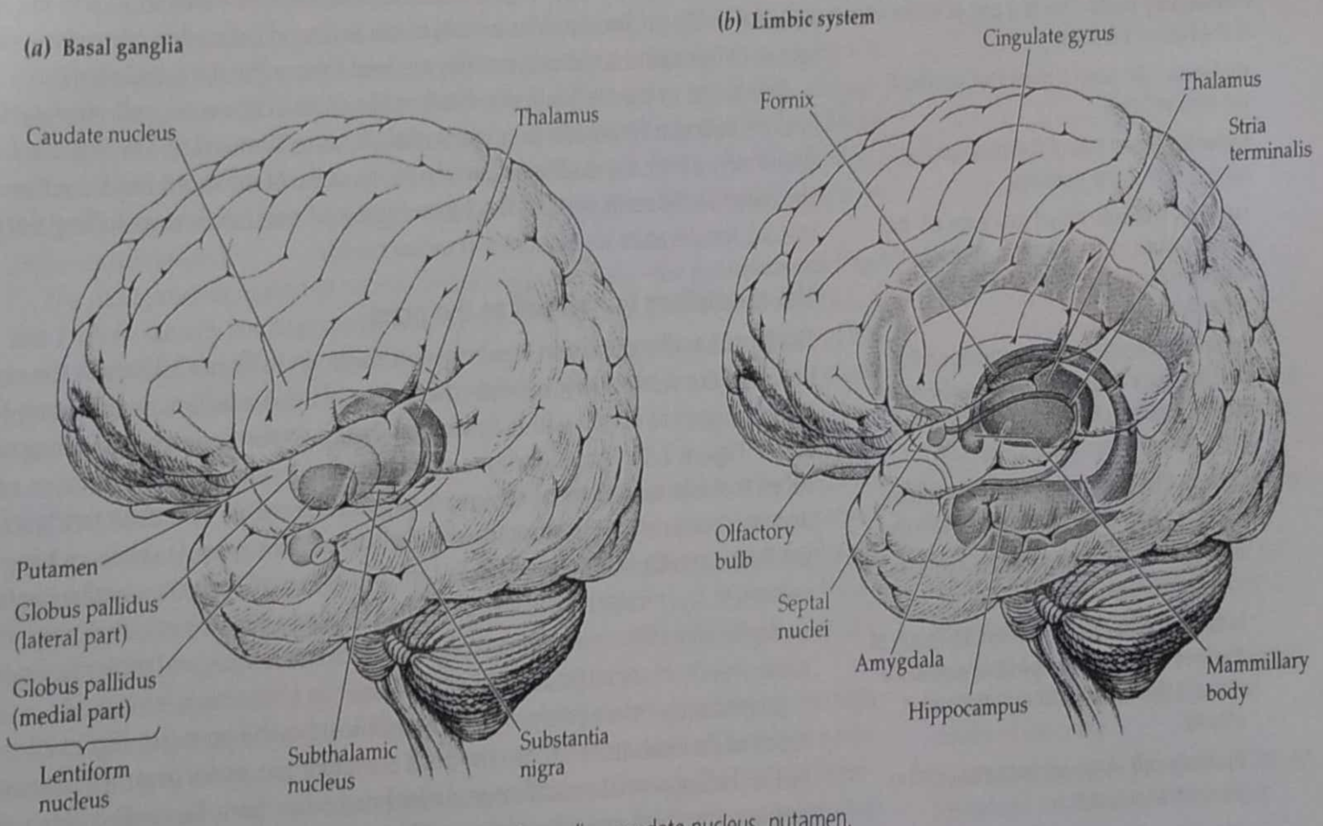
amygdala A group of nuclei in the medial anterior part of the temporal lobe.

hippocampus A medial temporal lobe structure that is thought to be important for learning and memory.

fornix A fiber tract that extends from the hippocampus to the mammillary body.

cingulate gyrus A cortical portion of the limbic system, found in the frontal and parietal midline.

olfactory bulb An anterior basal structure that receives olfactory (smell) inputs from the nasal cavaties.



2.15 Two Important Brain Systems (a) The basal ganglia—caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra—are important in movement. (b) The limbic system—hippocampus, cingulate gyrus, fornix, septal nuclei, stria terminalis, olfactory bulb, amygdala, and mammillary bodies—is important for emotion, learning, and memory.

The rest of the limbic system, including the hypothalamus and **mammillary bodies**, is found in the diencephalon.

The diencephalon is divided into thalamus and hypothalamus

The uppermost portion of the diencephalon is the **thalamus**, seen in the center of the adult brain in Figures 2.12*b*, 2.13*b*, and 2.15*b*. The thalamus is a complex cluster of nuclei that act as way stations to the cerebral cortex. Almost all sensory information enters the thalamus, where neurons send that information to the overlying cortex. The cortical cells in turn innervate the thalamus, controlling which sensory information is transmitted.

Because it is under the thalamus, the second part of the diencephalon is known as the **hypothalamus** (see Figure 2.12*b*). The hypothalamus is relatively small, but it is packed with many distinct nuclei that have vital functions. It has been implicated in hunger, thirst, temperature regulation, reproductive behaviors, and much more. The hypothalamus also controls the pituitary gland, which in turn controls almost all hormone secretion, as we'll learn in Chapter 5.

The midbrain has sensory and motor systems

The most prominent features of the midbrain are two pairs of bumps on the dorsal surface, one pair in each hemisphere. The more rostral bumps are the **superior colliculi** (singular *colliculus*), and the caudal bumps are the **inferior colliculi** (see Figure 2.12*b*); taken together the colliculi are referred to as the **tectum**. The superior colliculi process visual information; the inferior colliculi process information about sound.

Two important motor centers are embedded in the midbrain. One is the *substantia nigra*, which we mentioned as part of the basal ganglia (see Figure 2.15*a*), containing neurons that release the transmitter dopamine into the caudate (loss of this system leads to Parkinson's disease, discussed in Chapter 11). The other motor center is the **red nucleus** (named for its reddish tint), which communicates with motoneurons in the spinal cord. The midbrain also contains several nuclei that send their axons out to form cranial nerves. Other such cranial nerve nuclei are found throughout the brainstem.

Also found in the midbrain is a distributed network of neurons collectively referred to as the **reticular formation** (from the Latin *reticulum*, "network"). The reticular formation stretches from the midbrain down to the medulla. Many varied functions have been attributed to different parts of this loose aggregation of neurons, including sleep and arousal, temperature regulation, and motor control.

The cerebellum is attached to the pons

The lateral, midsagittal, and basal views of the brain in Figure 2.12 show the cerebellum. Like the cerebral hemispheres, the surface of the cerebellum is elaborately folded. The arrangement of cells within this folded sheet is relatively simple, consisting of three layers (**Figure 2.16**). A middle layer is composed of a single row of enormous neurons called **Purkinje cells** after the anatomist who first described their elaborate fan-shaped dendritic patterns. Axons from the small neurons of the **granule cell** layer, lying below the Purkinje cells, rise to the surface of the cerebellum to form the **parallel fibers** of the outermost layer (called the *molecular layer*). The cerebellum is particularly important for motor coordination and control, integration of some sensory and motor functions, and some aspects of cognition, including learning.

Immediately below (ventral to) the cerebellum lies the pons (see Figure 2.12*b* and *c*), a part of the brainstem. Within the pons are important motor control and sensory nuclei, including several cranial nerve nuclei. Information from the ear first enters the brain in the pons, via the nucleus of the vestibulocochlear (VIII) nerve.

The medulla maintains vital body functions

The medulla is the most caudal portion of the brainstem and marks the transition from brainstem to spinal cord. Within the medulla are the nuclei of cranial nerves XI and XII—

mammillary body One of a pair of nuclei at the base of the brain.

thalamus The brain regions that surround the third ventricle.

hypothalamus Part of the diencephalon, lying ventral to the thalamus.

superior colliculi Paired structures on the dorsal surface of the midbrain, rostral to the inferior colliculi, that receive visual information.

inferior colliculi Paired structures on the dorsal surface of the midbrain, caudal to the superior colliculi, that receive auditory information.

tectum The dorsal portion of the midbrain, including the inferior and superior colliculi.

red nucleus A brainstem structure related to motor control.

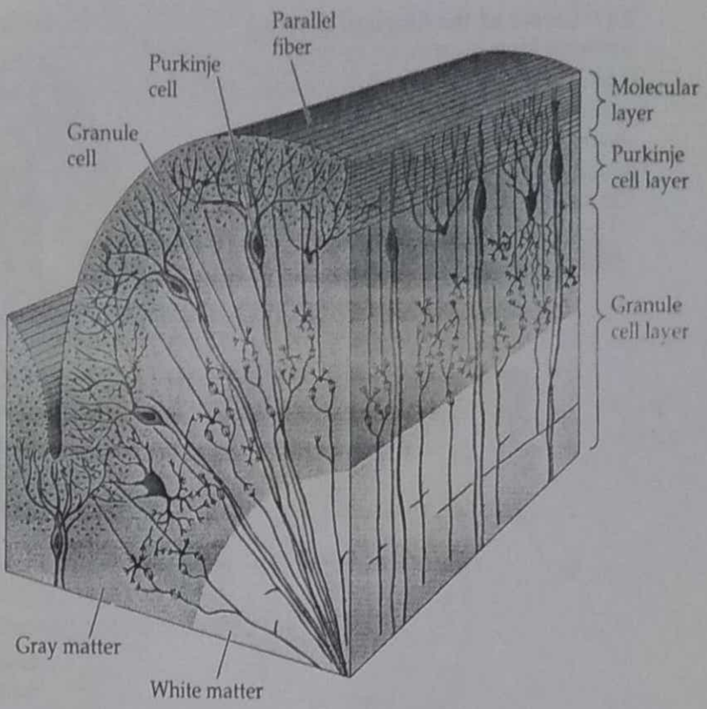
reticular formation An extensive region of the brainstem (extending from the medulla through the thalamus) that is involved in arousal.

Purkinje cell A type of large nerve cell in the cerebellar cortex.

granule cell A type of small nerve cell.

parallel fiber One of the axons of the granule cells that form the outermost layer of the cerebellar cortex.

cell bodies of neurons that control the neck and tongue muscles, respectively. The reticular formation, which we first saw in the midbrain, stretches through the pons and ends in the medulla. Because the medulla contains nuclei that regulate breathing and heart rate, tissue damage there is often fatal. All axons passing between the brain and spinal cord necessarily course through the medulla, and several medullary nuclei add their own axons to the descending-fiber tracts.



2.16 The Arrangement of Cells within the Cerebellum Large Purkinje cells dominate the cerebellum. Innervation between the various types of cells in the cerebellum forms a very consistent pattern. Cells depicted here in black inhibit the actions of other cells.

The cerebral cortex performs complex cognitive processing

Neuroscientists have long argued that understanding human cognition depends on unraveling the structure and fundamental functions of the cerebral cortex. If the cerebral cortex were unfolded, it would occupy an area of about 2000 cm^2 (315 square inches), more than three times the area of this book's cover. How are these cells arranged? And how do the arrangements allow for particular feats of human information processing?

The neurons of the cerebral cortex are arranged in six distinct layers (**Figure 2.17*a***). Tissue with this six-layered organization is referred to as **isocortex** (from the Greek *iso*, "same," and the Latin *cortex*, "bark of a tree"), or more simply as **cortex**, the term we will use in this book. (The alternate name *neocortex*—the Greek *neos* means "new"—is no longer favored because it implies that this tissue evolved more recently, a supposition for which there is no evidence.) Each cortical layer is distinct because it consists of either a band of similar neurons, or a particular pattern of dendrites or axons. For example, the outermost layer, layer I, is distinct because it has few cell bodies, and layers V and VI stand out because of their many neurons with large cell bodies. Some other telencephalic structures are made up of **allocortex** (from the Greek *allos*, "other"), tissue with three layers or unlayered organization (previously known as *archi-* or *paleocortex*).

The most prominent kind of neuron in the cerebral cortex—the **pyramidal cell** (**Figure 2.17*b***)—usually has its pyramid-shaped cell body in layer III or V. One dendrite of each pyramidal cell (called the **apical dendrite**) extends to the outermost surface of the cortex. The pyramidal cell also has several dendrites (called **basal dendrites**) that spread out horizontally from the cell body.

CORTICAL COLUMNS In some regions of the cerebral cortex, neurons are organized into regular columns, perpendicular to the layers, that seem to serve as cohesive information-processing units (Horton and Adams, 2005). These **cortical columns** extend through the entire thickness of the cortex, from the white matter to the surface. Within each column, most of the synaptic interconnections of neurons are vertical, although there are some horizontal connections as well (Mountcastle, 1979).

Cortical regions communicate with one another via tracts of axons looping through the underlying white matter (**Figure 2.18**). Some of these connections are short pathways to nearby cortical regions; others travel longer distances through the cerebral hemispheres. Some pathways link corresponding areas in the two hemispheres, traversing the corpus callosum to go from one hemisphere to the other. Some longer links between cortical regions involve multisynaptic chains of neurons that loop through subcortical regions such as the thalamus and the basal ganglia, allowing processing and integration of information at several levels.

isocortex (or cortex) Cerebral cortex that is made up of six distinct layers. (Formerly referred to as *neocortex*.)

allocortex Brain tissue with three layers or unlayered organization.

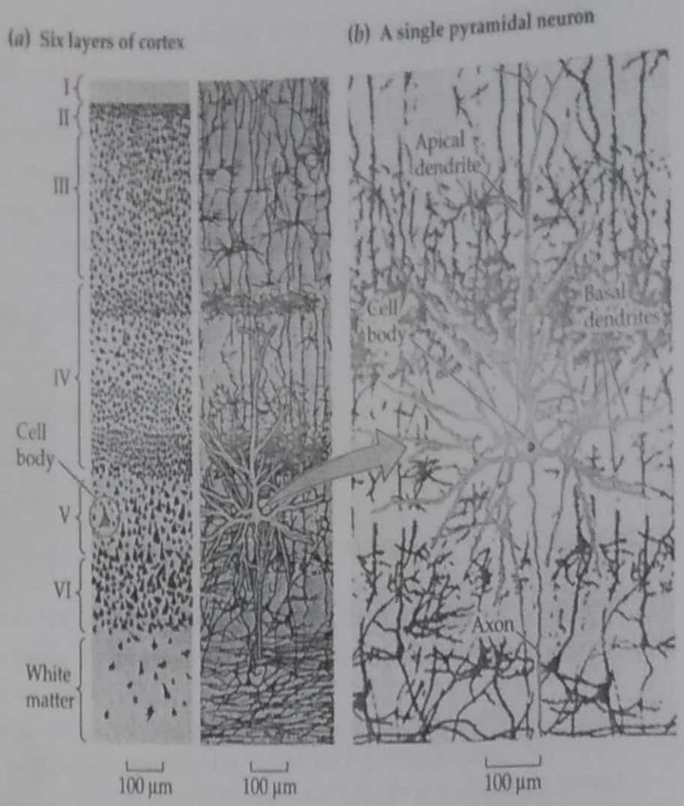
pyramidal cell A type of large nerve cell that has a roughly pyramid-shaped cell body; found in the cerebral cortex.

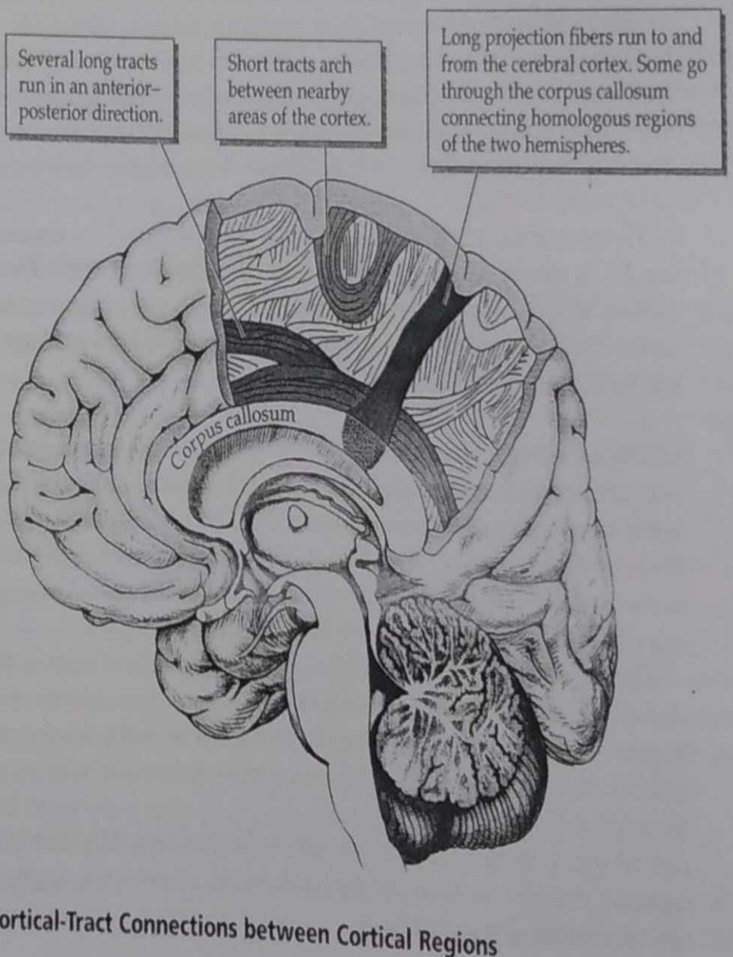
apical dendrite The dendrite that extends from a pyramidal cell to the outermost surface of the cortex.

basal dendrite One of several dendrites on a pyramidal cell that extend horizontally from the cell body.

cortical column One of the vertical columns that constitute the basic organization of the isocortex.

2.17 Layers of the Cerebral Cortex (a) The six layers of cortex can be distinguished with stains that reveal all cell bodies (left), or with stains that reveal a few neurons in their entirety (right). (b) This pyramidal cell has been enlarged about 100 times.


(a) Six layers of cortex
(b) A single pyramidal neuron
I
II
III
IV
Cell body
V
VI
White matter
Apical dendrite
Cell body
Basal dendrites
Axon
100 μm
100 μm
100 μm

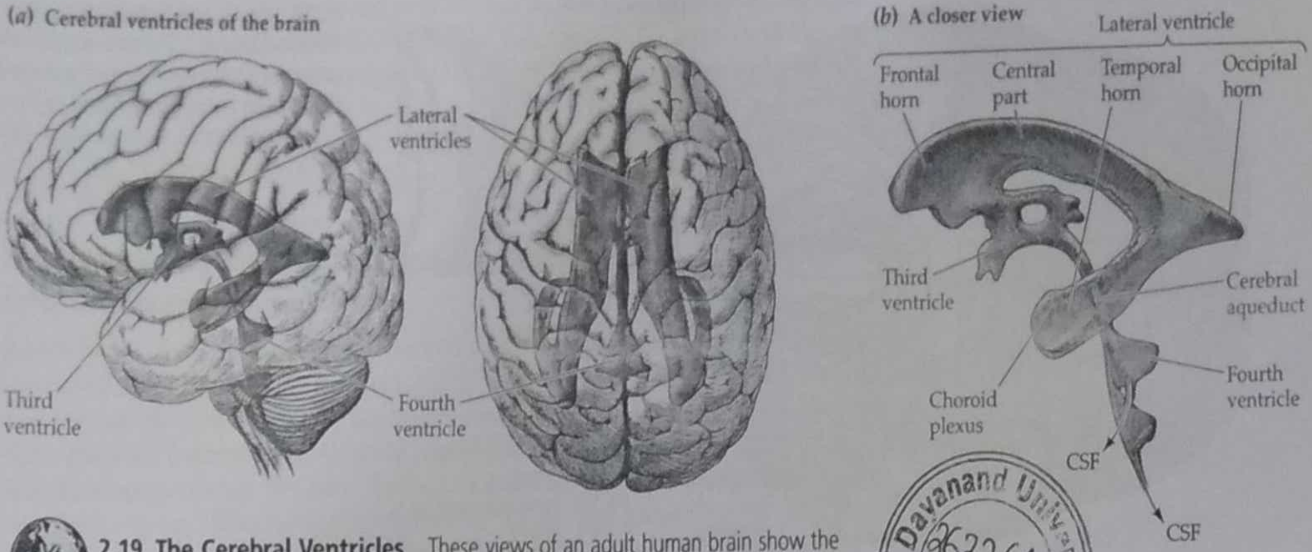

Several long tracts run in an anterior–posterior direction.

Short tracts arch between nearby areas of the cortex.

Long projection fibers run to and from the cerebral cortex. Some go through the corpus callosum connecting homologous regions of the two hemispheres.

Corpus callosum

2.18 Cortical-Tract Connections between Cortical Regions



2.19 The Cerebral Ventricles These views of an adult human brain show the position of the cerebral ventricles within it. Cerebrospinal fluid (CSF) is made in the lateral ventricles and exits from the fourth ventricle to surround the brain and spinal cord.

Maharishi Dayanand University Library ROHTAK 262266

Specialized Support Systems Protect and Nourish the Brain

Within the bony skull and vertebrae, the brain and spinal cord are surrounded by three protective membranes called **meninges** (see Figure 2.10). The tough outermost sheet is called the **dura mater** (in Latin, literally "hard mother"). The innermost layer, the delicate **pia mater** ("tender mother"), adheres tightly to the surface of the brain and follows all its contours. The weblike membrane between the dura mater and the pia mater is called the **arachnoid** (literally, "spiderweb-like"). Space within the arachnoid is filled with **cerebrospinal fluid** (**CSF**), a clear, colorless liquid. **Meningitis**, an inflammation of the meninges usually caused by viral infection, is a potentially lethal medical emergency characterized in early stages by headache, fever, and stiff neck.

The cerebral ventricles are chambers filled with fluid

Inside the brain is a series of chambers—the **ventricular system**—filled with CSF (**Figure 2.19**). The CSF circulating through the ventricular system has at least two main functions. First, it acts mechanically as a shock absorber for the brain: floating in CSF, the brain is protected from sudden movements of the head that would smash it against the inside of the skull. Second, CSF provides a medium for the exchange of materials, including nutrients, between blood vessels and brain tissue.

Each hemisphere of the brain contains a **lateral ventricle**, extending into all four lobes of the hemisphere. The lateral ventricles are lined with a specialized membrane called the **choroid plexus**, which produces CSF by filtering blood. CSF flows from the lateral ventricles into the **third ventricle**, which is located in the midline, and continues down a narrow passage to the **fourth ventricle**, which lies anterior to the cerebellum. Just below the cerebellum are three small openings through which CSF leaves the ventricular system to circulate over the outer surface of the brain and spinal cord. CSF is absorbed back into the circulatory system through large veins beneath the top of the skull.

The brain has an elaborate vascular system

Although it accounts for only 2% of the weight of the average human body, the brain consumes more than 20% of the body's energy. However, the brain has very little reserve of the basic metabolic fuels oxygen and glucose, and thus it depends critically on its blood supply to provide them (**Figure 2.20**). The **carotid arteries** ascend the left and right sides of the neck and branch into external and internal carotid arteries. The inter-

meninges The three protective sheets of tissue—dura mater, pia mater, and arachnoid—that surround the brain and spinal cord.

dura mater The outermost of the three meninges that surround the brain and spinal cord.

pia mater The innermost of the three meninges that surround the brain and spinal cord.

arachnoid The thin covering (one of the three meninges) of the brain that lies between the dura mater and pia mater.

cerebrospinal fluid (CSF) The fluid that fills the cerebral ventricles.

meningitis An acute inflammation of the meninges, usually caused by a viral or bacterial infection.

ventricular system A system of fluid-filled cavities inside the brain.

lateral ventricle A complexly shaped lateral portion of the ventricular system within each hemisphere of the brain.

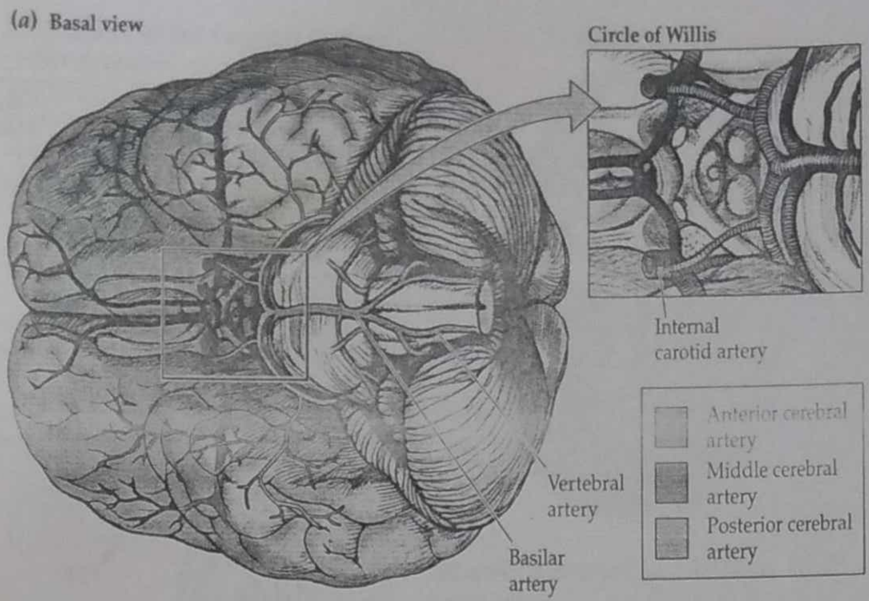
choroid plexus A highly vascular portion of the lining of the ventricles that secretes cerebrospinal fluid.

third ventricle The midline ventricle that conducts cerebrospinal fluid from the lateral ventricles to the fourth ventricle.

fourth ventricle The passageway within the pons that receives cerebrospinal fluid from the third ventricle and releases it to surround the brain and spinal cord.

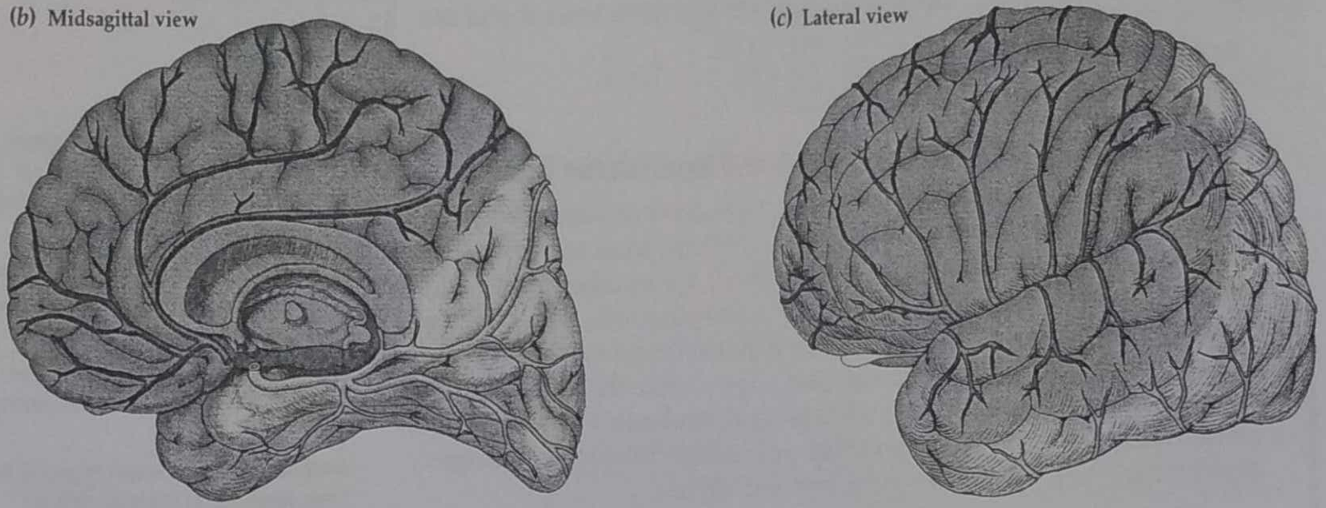
carotid arteries The major arteries that ascend the left and right sides of the neck to the brain.

(*a*) Basal view



(*b*) Midsagittal view

(*c*) Lateral view



2.20 The Blood Supply of the Human Brain The anterior, middle, and posterior cerebral arteries—the three principal arteries that provide blood to the cerebral hemispheres—are depicted here in basal (*a*), midsagittal (*b*), and lateral (*c*) views of the brain. The basilar and internal carotid arteries form a circle at the base of the brain known as the *circle of Willis*.

nal carotid artery enters the skull and branches into **anterior** and **middle cerebral arteries**, which supply blood to large regions of the cerebral hemispheres. The **vertebral arteries** ascend along the bony vertebrae and enter the base of the skull. They fuse to form the **basilar artery**, which runs along the ventral surface of the brainstem, with branches supplying blood to the structures of the hindbrain. The basilar artery also gives rise to the **posterior cerebral arteries**, which supply the posterior portions of the cerebral hemispheres.

At the base of the brain, the major cerebral arteries join to form a structure called the **circle of Willis** (see Figure 2.20*a*). This joining of arterial paths may provide an alternate route for blood flow if any of the main arteries to the brain should be damaged or blocked by disease. In **stroke**—one of the most prevalent causes of disability and death—insufficient blood flow to a region of the brain is caused by the blockage or rupture of blood vessels. Although the exact effects of stroke depend on the region of the brain that is affected, the five most common warning signs are sudden numbness or weakness, altered vision, dizziness, severe headache, and confusion or difficulty speaking. Effective treatments are available to help restore blood flow and minimize the long-term effects of a stroke, but only if the victim is treated immediately.

Fine arterioles branch off from the main arteries and in turn give rise to the very fine capillaries that deliver nutrients and other substances to brain cells and remove waste products. This exchange in the brain is quite different from

anterior cerebral arteries Two large arteries, arising from the internal carotids, that provide blood to the anterior poles and medial surfaces of the cerebral hemispheres.

middle cerebral arteries Two large arteries, arising from the internal carotids, that provide blood to most of the lateral surfaces of the cerebral hemispheres.

vertebral arteries Arteries that ascend the vertebrae, enter the base of the skull, and join together to form the basilar artery.

basilar artery An artery, formed by the fusion of the vertebral arteries, that supplies blood to the brainstem and to posterior portions of the cerebral hemispheres.

posterior cerebral arteries Two large arteries, arising from the basilar artery, that provide blood to posterior aspects of the cerebral hemispheres, cerebellum, and brainstem.

circle of Willis A structure at the base of the brain that is formed by the joining of the carotid and basilar arteries.

stroke Damage to a region of brain tissue that results from blockage or rupture of vessels that supply blood to that region.

exchanges between blood vessels and cells in other body organs. Because of very tight junctions between the cells that form their walls (endothelial cells), brain capillaries offer much greater resistance to the passage of large molecules across their walls than do capillaries found elsewhere in the body. This **blood–brain barrier** is thus a protective mechanism that may have evolved to help protect the brain from infections and blood-borne toxins, but it also makes the delivery of drugs to the brain more difficult.

Newer Imaging Techniques Allow Us to Look into the Living Human Brain

Researchers have long sought ways to peer into the living human brain to see structures and how they work during different behaviors. X-rays of the head are of limited usefulness because they cannot resolve the brain's small variations in density: X-ray photos of the brain are featureless. Attempts to improve contrast in X-rays through the injection of radiopaque (X-ray–blocking) dye led to a useful technique—the **angiogram** (from the Greek *angeion*, "blood vessel," and *gramma*, "record" or "picture")—that provides detailed views of the cerebral blood vessels and aids in the diagnosis of vascular disease. Although Wilder Penfield was able to make inferences about the functional organization of the brain by directly manipulating it during surgery, not until the advent of powerful computing techniques did the ability to visualize the form and functioning of the normal brain become a reality.

CT uses X rays to reveal brain structure

In **computerized axial tomography** (**CAT** or **CT**; from the Greek *tomos*, "crosscut" or "section"), X-ray energy is used to generate images. In a CT scanner, an X-ray source is moved by steps in an arc around the head. At each point, detectors on the opposite side of the head measure the amount of X-ray radiation that is absorbed; this value is proportional to the density of the tissue through which the X-rays passed. When this process is repeated from many angles and the results are mathematically combined, an anatomical map of the brain based on tissue density can be generated by the computer (**Figure 2.21*a***). CT scans are medium-resolution images, useful for visualizing problems such as strokes, tumors, or cortical atrophy. CT scanning has helped researchers identify brain regions that, when damaged, produce disorders of memory, language, attention, and other major cognitive functions.

MRI creates maps of the brain based on density

Magnetic resonance imaging (**MRI**) provides higher-resolution images that have replaced CTs for many applications. MRI images are derived from radio frequency energy, so an additional benefit is that patients are not exposed to potentially damaging X-rays. An MRI scan involves three main steps. First the patient's head is placed in an extremely powerful magnet that causes all the protons in the brain's tissues to line up in parallel, instead of in their usual random orientations (protons are the nuclei of hydrogen atoms and thus abundant in water). Next the protons are knocked over by a powerful pulse of radio waves. Then, when this pulse is turned off, the protons relax back to their original configuration, emitting radio waves as they go. The emitted radio frequency energy, measured by detectors ringing the head, differs for tissues of varying densities. A powerful computer compiles this density-based information to generate a detailed cross-sectional view of the brain (**Figure 2.21*b***) (Elster and Burdette, 2001). With their higher resolution, MRI images can reveal subtle changes in the brain, such as the local demyelination that is characteristic of multiple sclerosis.

PET maps radioactive tracers to produce images of brain activity

In **positron emission tomography** (**PET**) the objective is to obtain images of the brain's *activity*, rather than details of its *structure*, and it has proven to be very valuable for both experimental and diagnostic purposes. Short-lived radioactive chemicals are injected into the bloodstream, and a ring of detectors maps the destination of these chemicals

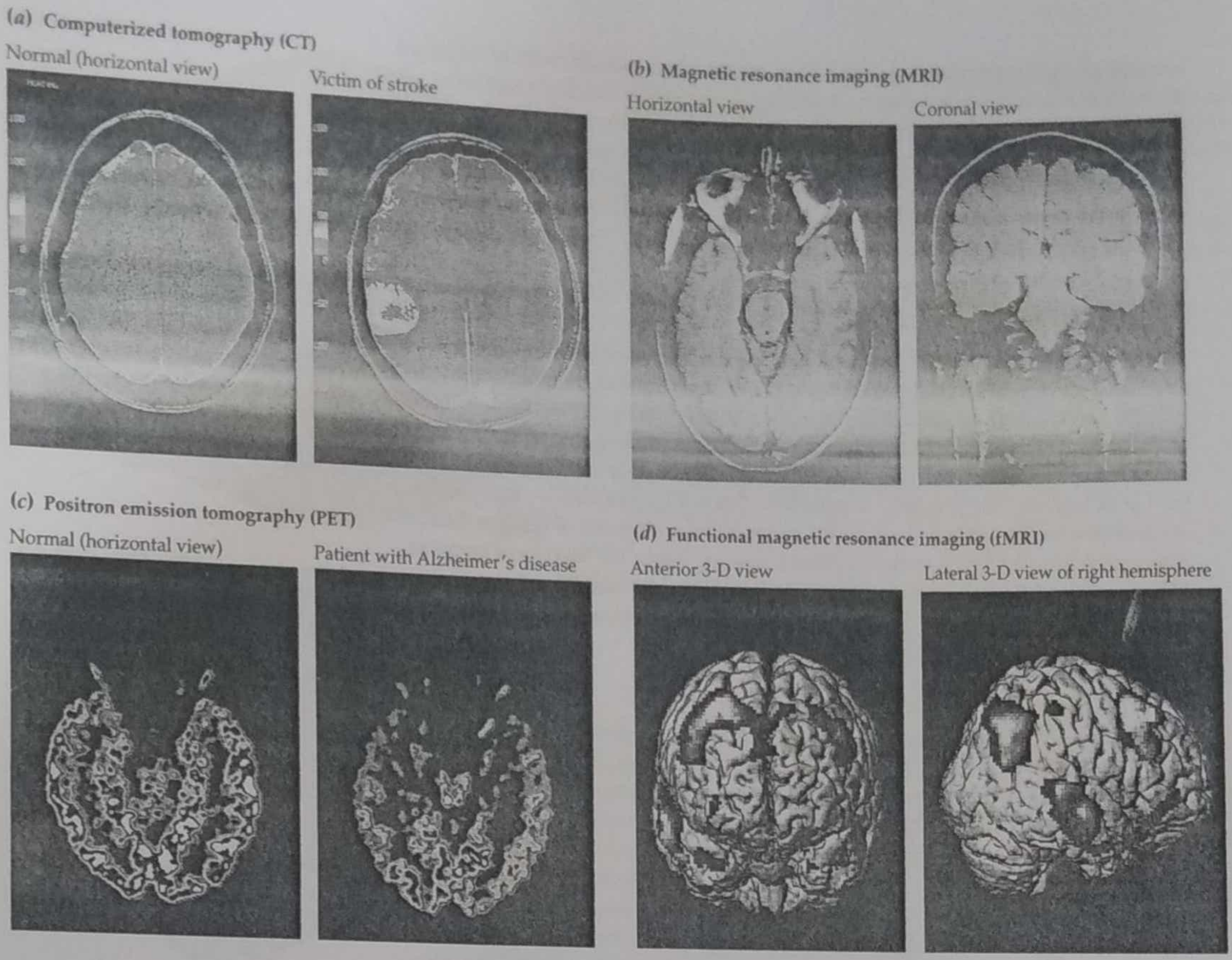
blood–brain barrier The mechanisms that make the movement of substances from capillaries into brain cells more difficult than exchanges in other body organs.

angiogram A specialized X-ray image of the head, taken shortly after the cerebral blood vessels have been filled with a radiopaque dye by means of a catheter.

computerized axial tomography (CAT or CT) A noninvasive technique for examining brain structure in humans through computer analysis of X-ray absorption at several positions around the head.

magnetic resonance imaging (MRI) A noninvasive technique that uses magnetic energy to generate images that reveal some structural details in the living brain.

positron emission tomography (PET) A technique for examining brain function by combining tomography with injections of radioactive substances used by the brain.


(a) Computerized tomography (CT)
Normal (horizontal view)
Victim of stroke
(b) Magnetic resonance imaging (MRI)
Horizontal view
Coronal view
(c) Positron emission tomography (PET)
Normal (horizontal view)
Patient with Alzheimer's disease
(d) Functional magnetic resonance imaging (fMRI)
Anterior 3-D view
Lateral 3-D view of right hemisphere

2.21 Visualizing the Living Human Brain The images obtained from some important brain-imaging techniques. (*a*) CT scans from a normal individual and from a patient who suffered a stroke; the stroke lesion is visible as a large yellow area. (*b*) Horizontal and coronal MRI images of a normal human brain. Note the clarity in the definition of gyri and sulci of the cerebral cortex. (*c*) PET scans from a normal human and a patient with Alzheimer's, showing levels of metabolic activity in the brain. Note the greater level of activity in the normal brain. (*d*) Functional-MRI images showing changes in regional brain metabolism recorded during the presentation of visual or auditory stimuli. The images are three-dimensional renderings showing areas where brain activity changed in subjects viewing images of their romantic partner (see Figure 1.6). (Images in *d* courtesy of Semir Zeki.)

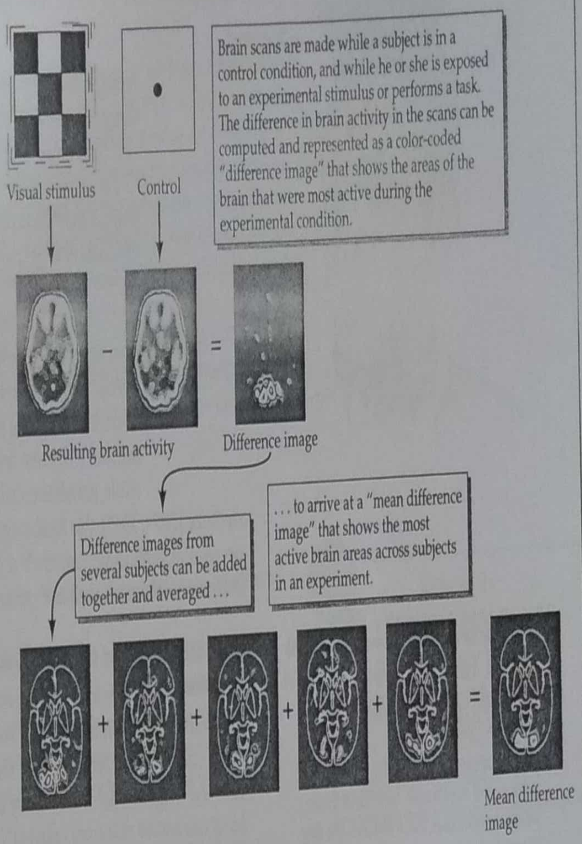
in the brain by sensing their emissions of radiation. In one common technique, radioactive glucose is administered while a subject is performing a specific cognitive task. Because the radioactive glucose is particularly taken up and used by the brain regions that are most active from moment to moment, a computer-generated color-coded portrait of brain activity can be created (**Figure 2.21c**) (P. E. Roland, 1993). Through precise experimental control and the use of special mathematical techniques (described in **Box 2.3**), we can generate metabolic maps of the brain that identify which brain regions contribute to specific functions.

functional MRI (fMRI) Magnetic resonance imaging that detects changes in blood flow and therefore identifies regions of the brain that are particularly active during a given task.

Functional MRI uses local changes in metabolism to identify active brain regions

First introduced in the 1990s, **functional MRI** (**fMRI**) has revolutionized cognitive neuroscience research, producing images with reasonable speed (temporal resolution) and

BOX 2.3 Isolating Specific Brain Activity



Brain scans are made while a subject is in a control condition, and while he or she is exposed to an experimental stimulus or performs a task. The difference in brain activity in the scans can be computed and represented as a color-coded "difference image" that shows the areas of the brain that were most active during the experimental condition.

Difference images from several subjects can be added together and averaged . . .

. . . to arrive at a "mean difference image" that shows the most active brain areas across subjects in an experiment.

The advent of modern brain imaging has enabled dramatic images of the brain showing the particular brain regions that are activated during specific cognitive processes; there are many such images in this book. But, as you might expect, in a normal person almost all of the brain is active at any given moment. So how do we get these highly specific images of brain activity?

The PET scan shown here beneath the box labeled "Visual stimulus" was made while a person looked at a fixation point surrounded by a flickering checkerboard ring. The scan next to it (beneath the box labeled "Control") was made while a person looked at a fixation point alone. In a comparison of the two, it is hard to see differences, but subtracting the control values from the stimulation values yields an image such as that shown at the upper right ("Difference image"); in this scan it is easy to see that the main difference in activity is in the posterior part of the brain (the visual cortex).

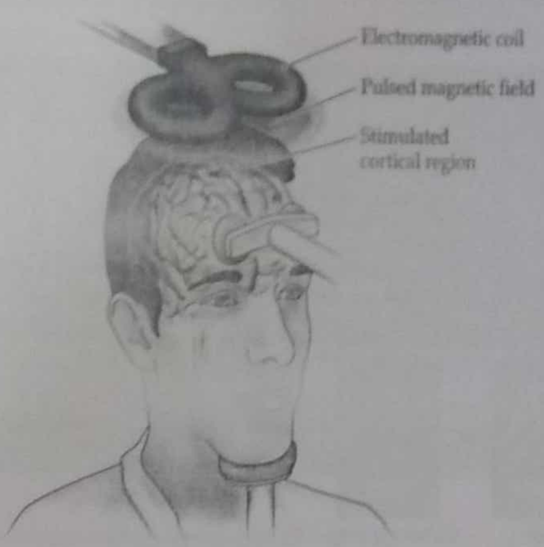
The PET scans shown in the bottom row are difference images for five individuals who performed the same two stimulation and control tasks. Averaging these five scans yields the mean difference image for all five subjects that is shown at far right. Averaged images yield more-reliable results than individual images, but they lack some of the specificity of the individual images. (PET scans courtesy of Marcus Raichle.)

excellent sharpness (spatial resolution). Although the basic technology is the same as for MRI scanning (described above), it is applied differently. In fMRI scanning, high-powered, rapidly oscillating magnetic-field gradients are used to detect small changes in brain metabolism, particularly oxygen use by the most active regions of the brain, rather than structural information. As with PET, scientists can use fMRI data to create images that reflect the activity of different parts of the brain while people engage in various experimental tasks (**Figure 2.21*d***). The detailed activity maps provided by fMRI reveal how networks of brain structures collaborate on complex cognitive processes. Interestingly, it appears that the fMRI image generally reflects synaptic inputs and local processing, rather than the production of neural impulses (Logothetis, 2003), and is altered by aging and disease states (D'Esposito et al., 2005). Identification of technical issues like these helps researchers to be more accurate in interpreting image data.

Optical imaging uses near-infrared light to visualize brain activity

Other investigators are using light to make images of brain activity within the head (Gratton and Fabiani, 2001; Villringer and Chance, 1997). In **optical imaging**, researchers capitalize on the observation that near-infrared light (wavelengths of 700 to 1000 nm) passes easily through skin, scalp, and skull and penetrates a short distance into the cortex. When such light is transmitted into the brain and detectors pick up the reflections

optical imaging A method for visualizing brain activity in which near-infrared light is passed through the scalp and skull.



2.22 Transcranial Magnetic Stimulation Magnetic fields induced by electromagnetic coils stimulate neurons of the underlying cortical surface.

through the scalp, the responses reveal the activity of cortical regions. Some components of the optical responses represent the electrical signals of neurons, and other components represent blood flow.

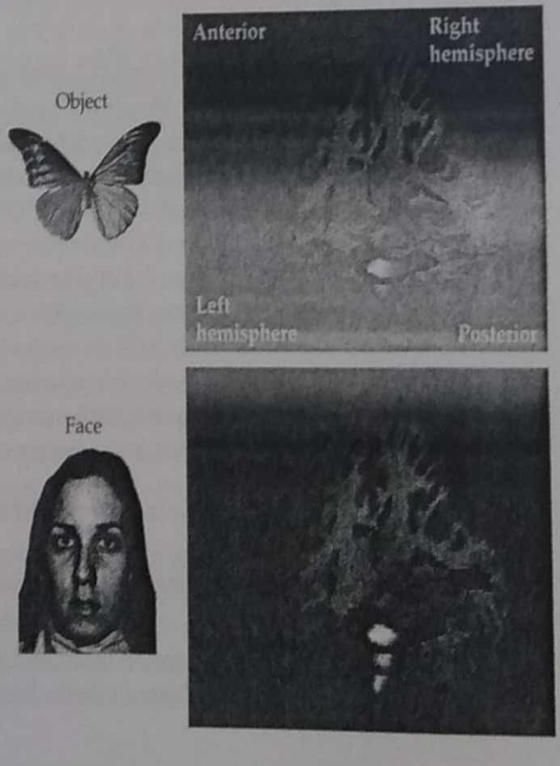
The relatively low expense and small size of the optical imaging apparatus may allow many more laboratories to use brain imaging in their research. And because optical imaging is based on light, it is ideal for simultaneous use with other techniques; optical imaging has been coupled with transcranial magnetic stimulation (TMS; Figure 2.22), in which focal magnetic currents are used to briefly stimulate the cortex of alert normal subjects directly, without a hole having to be made in the scalp or skull (Y. Noguchi et al., 2003). This approach allows experimenters to activate a discrete area of the brain through electromagnetic induction while simultaneously mapping the resulting pattern of activation. In *repetitive TMS* (*rTMS*), this focal magnetic stimulation of the brain is cycled several times per second, producing transient but measurable changes in behavior that may be of use in clinical settings, as well as in research.

transcranial magnetic stimulation (TMS) Localized, noninvasive stimulation of cortical neurons through the application of strong magnetic fields.

magnetoencephalography (MEG) A passive and noninvasive functional brain-imaging technique that measures the tiny magnetic fields produced by active neurons, in order to identify regions of the brain that are particularly active during a given task.

MEG creates maps of brain function from the tiny magnetic fields of active neurons

Magnetism and brain function are linked in another way too. Like any electrical system, active circuits of the brain produce their own magnetic fields. Although they are minuscule, the magnetic fields created by activity in local circuits of neurons can be detected by ultrasensitive detectors called *SQUIDs* (*superconducting quantum interference devices*). In **magnetoencephalography** (**MEG**), a large array of SQUIDs is used to create real-time maps of brain activity from localized cortical magnetic fields during ongoing cognitive processing (**Figure 2.23**). Because the temporal resolution of MEG is so good—it responds very quickly to moment-by-moment changes in brain activity—it is excellent for studying rapidly shifting patterns of brain activity in cortical circuits, particularly when



2.23 Animal Magnetism Using measurements of the miniscule magnetic fields given off by ensembles of cortical cells during specific behavioral functions, magnetoencephalography (MEG) provides a real-time map of brain activity. In this image, MEG data have been superimposed on a structural MRI of a subject's brain, creating a map of brain activity associated with viewing faces versus non-face objects. (Image courtesy of Drs. Mario Liotti and Anthony Herdman, Simon Fraser University, and Down Syndrome Research Foundation).

used in conjunction with MRI (Lin et al., 2004). Like optical imaging, MEG is noninvasive and thus suitable for studies of infants and children.

Sophisticated imaging techniques overcome some of the limitations on other sources of evidence

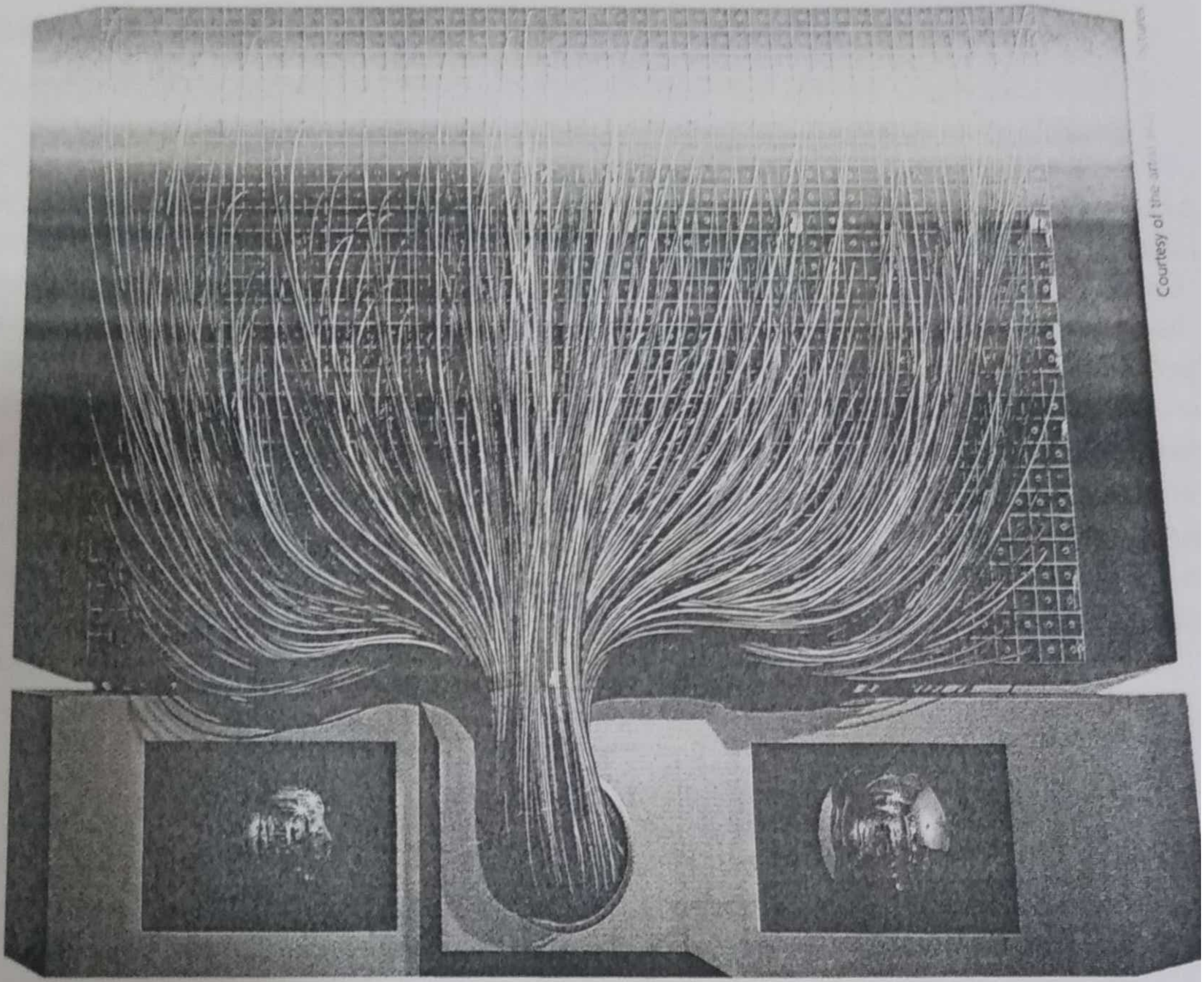
To investigate many problems of biological psychology, imaging provides evidence to supplement studies of naturally occurring or experimental brain lesions. Each of these kinds of investigation helps overcome limitations on the other sources of evidence. It has been said that "remarkable progress in brain imaging techniques does not compete with the psychological analysis of behavior but instead places a new premium upon the thoughtfulness and accuracy of such analysis" (Gabrieli, 1998, p. 89). However, it is important to keep in mind that although functional brain images seem unambiguous and easy to label, they are subject to a variety of procedural and experimental limitations (Racine et al., 2005). In particular, they are not actual images of the brain, but rather computer-generated composites based on selected measurements of neural function, such as the metabolism and electrical activity of neurons. The origins of these neural signals are the topic of the next chapter.

Summary

1. The nervous system is extensive—monitoring, regulating, and modulating the activities of all parts and organs of the body.
2. At the microscopic level, neurons are the basic units of the nervous system. The typical neuron of most vertebrate species has four main parts: (1) the cell body, which contains the nucleus; (2) dendrites, which receive information; (3) an axon, which carries impulses from the neuron; and (4) axon terminals, which transmit the neuron's impulses to other cells. Because of the variety of functions they serve, neurons are extremely varied in size, shape, and chemical activity.
3. The axon is generally tubular, branching at the end into many collaterals. Axonal transport is the movement of materials within the axon.
4. In order to process information, neurons arrange themselves into computational ensembles. Neurons make functional contacts with other neurons, or with muscles or glands, at specialized junctions called synapses. Synapses may be made onto dendritic spines, which exhibit neuroplasticity, changing shape in response to experience.
5. At most synapses a chemical transmitter liberated by the presynaptic terminal diffuses across the synaptic cleft and binds to special receptor molecules in the postsynaptic membrane.
6. Glial cells serve many functions, including the breakdown of transmitters, the production of myelin sheaths around axons, the exchange of nutrients and other materials with neurons, the direct regulation of the interconnections and activity of neurons, and the removal of cellular debris.
7. At the gross anatomical level (i.e., to the naked eye), the nervous system of vertebrates is divided into peripheral and central nervous systems.
8. The peripheral nervous system includes the cranial nerves, spinal nerves, and autonomic nervous system. The autonomic nervous system consists of the sympathetic nervous system, which tends to ready the body for action; the parasympathetic nervous system, which tends to have an effect opposite to that of the sympathetic system; and the enteric nervous system, which innervates the gut.
9. The central nervous system (CNS) consists of the brain and spinal cord. The main divisions of the brain can be seen most clearly in the embryo. These divisions are the forebrain (telencephalon and diencephalon), the midbrain (mesencephalon), and the hindbrain (metencephalon and myelencephalon).
10. The human brain is dominated by the cerebral hemispheres, which include the cerebral cortex, an extensive sheet of folded tissue. The cerebral cortex is responsible for higher-order functions such as vision, language, and memory. Other neural systems include the basal ganglia, which regulate movement; the limbic system, which controls emotional behaviors; and the cerebellum, which aids motor control.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

CHAPTER 3



Courtesy of the artist

Robert Longo, HUM (Making Ourselves), 19

CONTENTS

Electrical Signals Are the Vocabulary of the Nervous System 59

The Sequence of Transmission Processes at Chemical Synapses 75

Neurons and Synapses Combine to Make Circuits 80

Gross Electrical Activity of the Human Brain

Neurophysiology: The Generation, Transmission, and Integration of Neural Signals

Finding an Answer in a Heartbeat

In the early twentieth century, debate raged over the basic nature of neural communication. The discovery that individual nerve cells contacted each other at thousands of points was fresh knowledge. What happened at these synapses? Did an electrical current pass between the cells? Might information instead take the form of a mysterious substance, wafting across the synapse from one cell to the other? A definitive answer to these questions seemed beyond the reach of the available technology.

A solution came to Otto Loewi (1873–1961) in a dream one night in 1921: a simple experiment that would definitively discriminate between the two candidate modes of transmission—chemical versus electrical. In excitement, Loewi sat up in bed and scribbled a few notes, but in the morning he was disappointed to find the notes indecipherable. When the dream came again the following night, Loewi got up and went straight to the lab, where he performed the experiment while it was still fresh in his mind.

An eminent physiologist, Loewi had recently been studying cardiac function in frogs. So he applied electrical stimulation to the vagus nerve of a frog, which he knew would decrease its heart rate, and collected a sample of the fluid that bathed the frog's heart. Then he bathed a second frog's heart with the sample from the first frog. When the second frog's heart also slowed, Loewi knew that he had a solution to the riddle of synaptic transmission. The stimulation of th first frog's nerve must have caused the release of a diffusib chemical—what Loewi initially called *Vagusstoff* ("substan from the vagus")—into the fluid. It was a breakthrough fo which Loewi would receive a Nobel Prize in 1936.

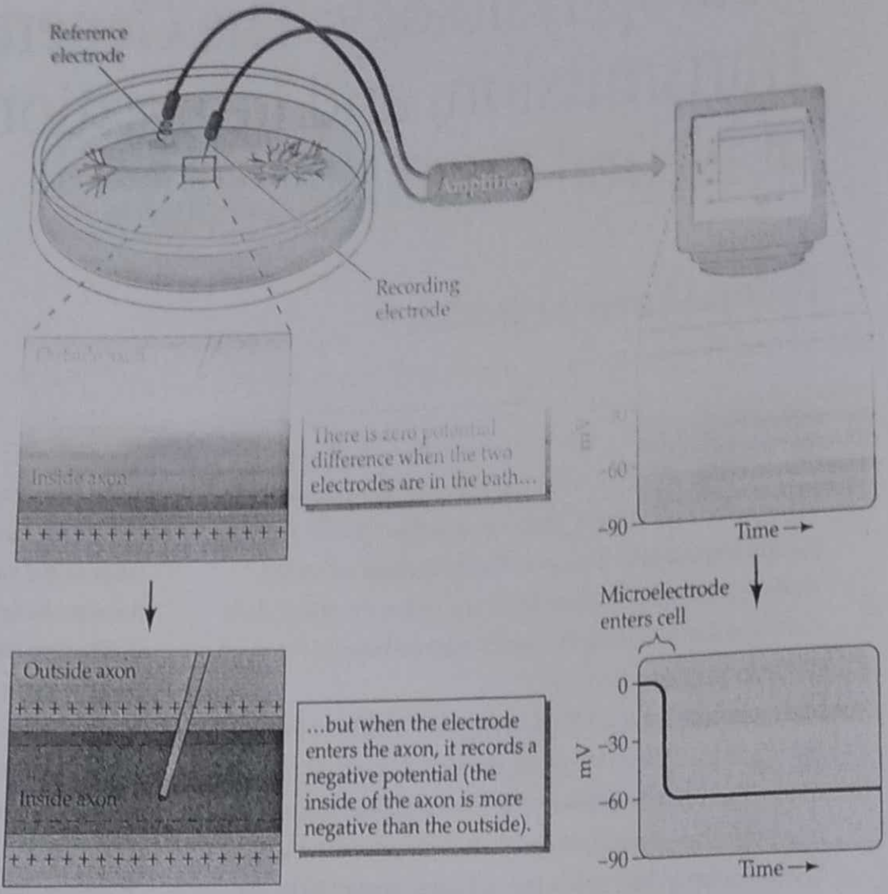
Only through the stimulation of nerves can we perceive the world. As you read this page, light stimulates your eye and starts a barrage of signals that race along nerve cells to your brain. As these impulses spread through your cerebral circuitry, larger-scale bursts of neural activity produce the conscious experience of reading. The simultaneous activation of related thoughts and memories stored within your brain produces your unique response to the information on this page. In this chapter we delve into the electrochemical properties of neurons that allow them to encode information in the form of electrical signals. We then turn to the chemical transmission of information across synapses, and the basic forms of information processing accomplished by ensembles of neurons.

Electrical Signals Are the Vocabulary of the Nervous System

All living cells possess an electrical charge—they are more negative on the inside than on the outside—that is a legacy of their evolutionary origins. Early single-celled organisms living in the primordial sea contained many proteins, which are negatively charged. Long ago, nerve cells began to exploit this property to communicate with one another. In this chapter we'll learn how one neuron transmits information to another neuron by producing a local, temporary change in the target neuron's polarity. The target neuron integrates a multitude of these inputs to decide whether to fire its own signal, ultimately altering the polarity of yet other neurons.

The bioelectrical neural communication system works in much the same way in animals as diverse as human beings, insects, and jellyfish. These neural signals underlie the whole range of thought and action, from composing music or solving a mathematical problem to feeling an itch on the skin and swatting a mosquito. To understand this

3.1 Measuring the Resting Potential


Reference electrode
Amplifier
Recording electrode
Outside axon
Inside axon
There is zero potential difference when the two electrodes are in the bath...
mV
-30
-60
-90
Time
Microelectrode enters cell
Outside axon
Inside axon
...but when the electrode enters the axon, it records a negative potential (the inside of the axon is more negative than the outside).
0
-30
-60
-90
mV
Time

system, we'll first review the physical forces at work, then discuss some details of why nerve cells are electrically polarized, how one neuron influences the polarity of others, and how a change of polarity in one part of a neuron can spread throughout that cell.

A balance of electrochemical forces produces the resting membrane potential of neurons

Let's start by considering a neuron at rest, neither perturbed by other neurons nor producing its own signals. Of the many **ions** (electrically charged molecules) that a neuron contains, a majority are **anions** (negatively charged ions), especially large protein anions that cannot exit the cell. Neurons contain relatively fewer **cations** (positively charged ions). All of these ions are dissolved in an intracellular fluid, which is separated from the extracellular fluid by a cell membrane.

If we insert a fine **microelectrode** into the interior of a neuron and compare it to the extracellular fluid (as illustrated in **Figure 3.1**), we find that the neuron is more negative on the inside than on the outside. Specifically, a neuron at rest exhibits a characteristic **resting membrane potential** (an electrical-potential difference across the membrane) of about –50 to –80 thousandths of a volt (–50 to –80 **millivolts** [**mV**]; the negative sign indicates the **negative polarity** of the cell's interior). To fully understand the basis of this membrane potential, we have to consider some special properties of the cell membrane, as well as two forces that act to drive ions across it.

Cell membranes are made up of a **lipid bilayer**—two layers of linked fatty molecules (see Figure 3.4)—within which many sorts of specialized proteins "float." One important type of membrane-spanning protein is the **ion channel**, a tubelike pore that allows ions of a specific type to pass through the membrane. As we'll see later, some types of ion channels are **gated** and can open and close rapidly in response to changes in volt-

ion An atom or molecule that has acquired an electrical charge by gaining or losing one or more electrons.

anion A negatively charged ion, such as a protein or chloride ion.

cation A positively charged ion, such as a potassium or sodium ion.

intracellular fluid Also called *cytoplasm*. The watery solution found within cells.

extracellular fluid The fluid in the spaces between cells (interstitial fluid) and in the vascular system.

cell membrane The lipid bilayer that ensheathes a cell.

microelectrode An especially small electrode used to record electrical potentials from living cells.

resting membrane potential A difference in electrical potential across the membrane of a nerve cell during an inactive period.

millivolt (mV) A thousandth of a volt.

negative polarity A negative electrical-potential difference relative to a reference electrode.

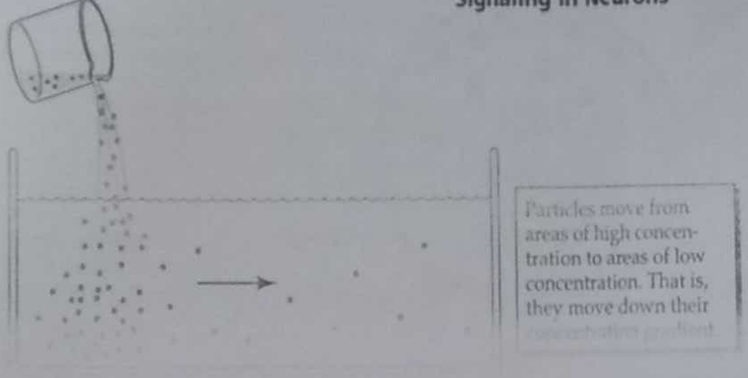
lipid bilayer The structure of the neuronal cell membrane, which consists of two layers of lipid molecules, within which float various specialized proteins, such as receptors.

ion channel A pore in the cell membrane that permits the passage of certain ions through the membrane when the channels are open.

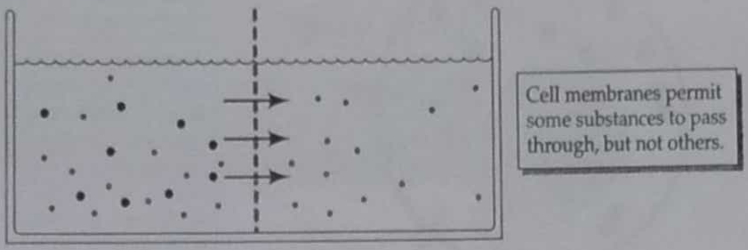
gated Referring to the property by which an ion channel may be opened or closed by factors such as chemicals, voltage changes, or mechanical actions.

3.2 Ionic Forces Underlying Electrical Signaling in Neurons

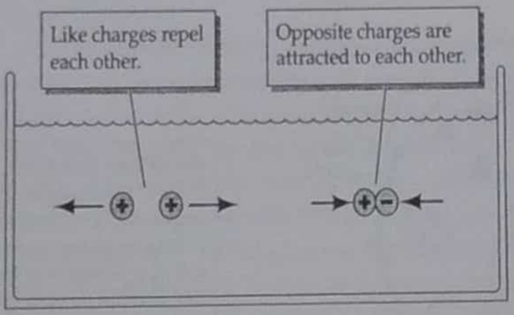
(a) Diffusion


Particles move from areas of high concentration to areas of low concentration. That is, they move down their concentration gradient.

(b) Diffusion through semipermeable membranes


Cell membranes permit some substances to pass through, but not others.

(c) Electrostatic forces


Like charges repel each other.
Opposite charges are attracted to each other.

age, to the presence of certain chemicals, or to mechanical deflection of the cell membrane. But some ion channels stay open all the time, and the cell membrane of a neuron contains many such channels that selectively allow only **potassium ions** (K^+) to cross the membrane. Because it is studded with these K^+ channels, we say that the cell membrane of a neuron exhibits **selective permeability** (Figure 3.2*b*) to potassium; that is, K^+ ions (but not other types of ions) can enter or exit the cell fairly freely, unimpeded by the cell membrane.

The resting potential of the neuron reflects a balancing act between two opposing forces that drive ions in and out of the neuron. The first of these is **diffusion** (Figure 3.2*a*), which is the force that causes molecules of a substance to diffuse from regions of high concentration to regions of low concentration. For example, if a drop of food coloring is placed in a glass of water, the molecules of dye tend to move from the drop, where they are highly concentrated, into the rest of the glass, where they are less concentrated. In other words, molecules tend to move down their **concentration gradient** until they are evenly distributed.

The second force at work is **electrostatic pressure** (Figure 3.2*c*), which arises from the distribution of electrical charges rather than the distribution of molecules. Charged particles exert electrical force on one another: like charges repel, and opposite charges attract. Positively charged cations are thus attracted to the negatively charged interior of

potassium ion (K^+) A potassium atom that carries a positive charge because it has lost one electron.

selective permeability The property of a membrane that allows some substances to pass through, but not others.

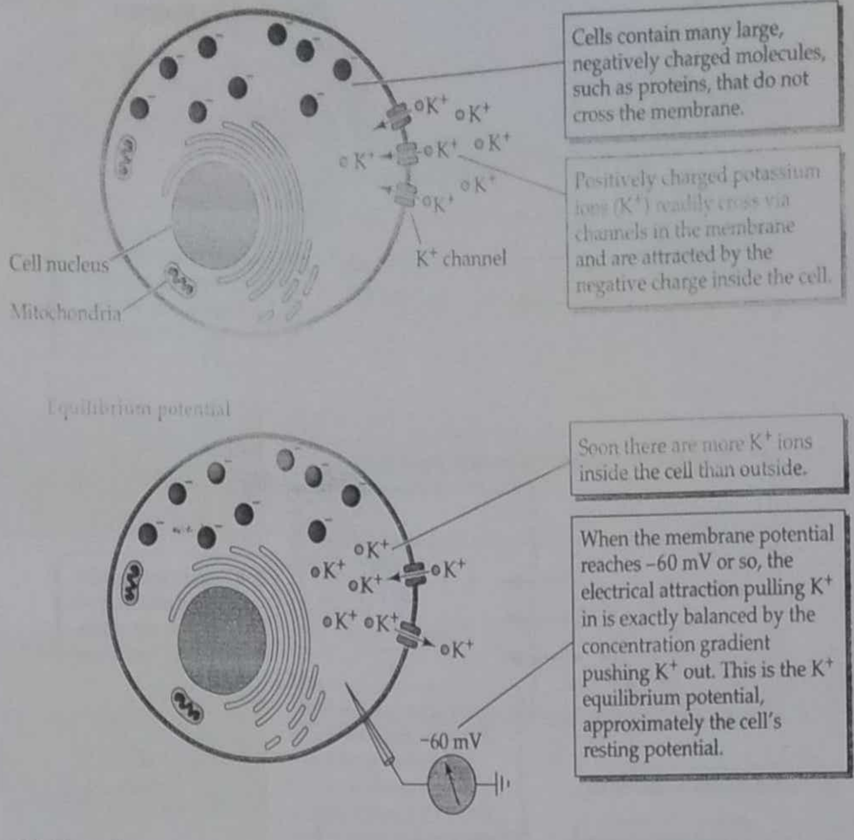
diffusion The spontaneous spread of molecules of one substance among molecules of another substance until a uniform concentration is achieved.

concentration gradient Variation of the concentration of a substance within a region.

electrostatic pressure The propensity of charged molecules or ions to move, via diffusion, toward areas with the opposite charge.

3.3 The Ionic Basis of the Resting Potential

(*a*) **Membrane permeability to ions**



Cells contain many large, negatively charged molecules, such as proteins, that do not cross the membrane.

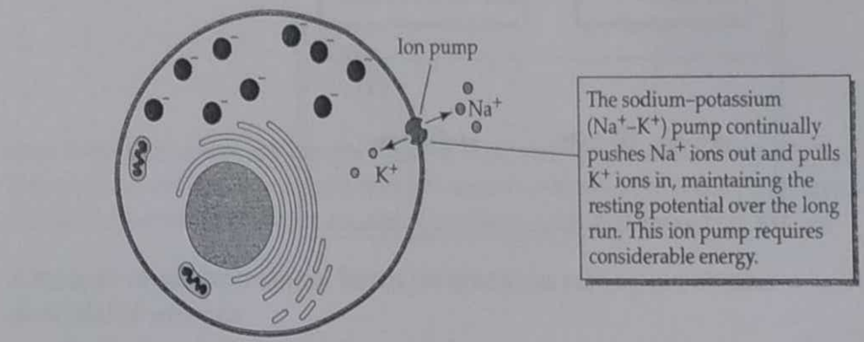
Positively charged potassium ions (K⁺) readily cross via channels in the membrane and are attracted by the negative charge inside the cell.

Equilibrium potential

Soon there are more K⁺ ions inside the cell than outside.

When the membrane potential reaches −60 mV or so, the electrical attraction pulling K⁺ in is exactly balanced by the concentration gradient pushing K⁺ out. This is the K⁺ equilibrium potential, approximately the cell's resting potential.

(*b*) **The sodium–potassium pump**



The sodium–potassium (Na⁺–K⁺) pump continually pushes Na⁺ ions out and pulls K⁺ ions in, maintaining the resting potential over the long run. This ion pump requires considerable energy.

the cell; and conversely, anions are repelled by the cell interior and so tend to exit to the extracellular fluid.

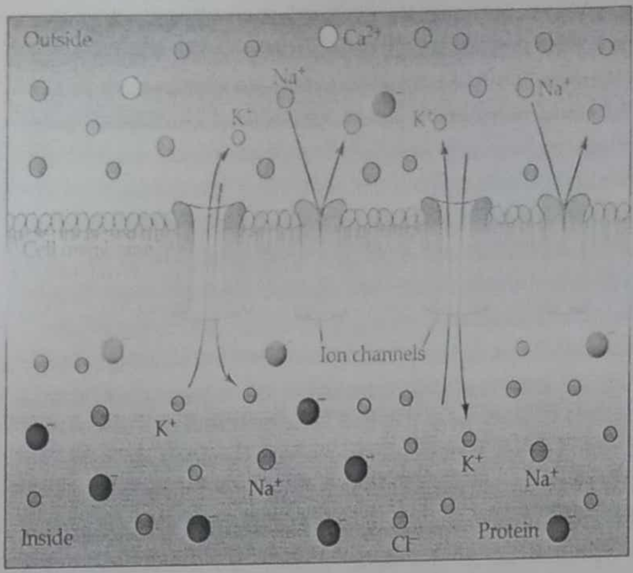
Now let's consider the situation across a neuron's cell membrane. Recall that, at rest, it is selectively permeable to K⁺. Electrostatic pressure tends to pull positively charged K⁺ ions into the neuron's negatively charged interior. As a result, however, the concentration of K⁺ ions on the inside of the cell steadily increases relative to the outside, and thus the concentration gradient for K⁺ increasingly pushes K⁺ ions *out* of the cell. Eventually the opposing forces exerted by the K⁺ concentration gradient and by electrostatic pressure reach **equilibrium**, exactly balancing each other: any further movement of K⁺ ions into the cell is matched by the flow of K⁺ ions out of the cell. This point corresponds to the cell's resting membrane potential of about −60 mV (values may range between −50 and −80 mV). **Figure 3.3a** depicts this process.

The **Nernst equation** is a mathematical function describing the voltage that develops when a semipermeable membrane separates different concentrations of ions. The equation's prediction of the resting membrane potential of neurons is *almost* perfect, but it yields a slight overestimation. What is the basis of the discrepancy? The predicted value differs from the observed value because the membrane is not absolutely impermeable

equilibrium In chemistry, the point at which all ongoing reactions are canceled or balanced by others, resulting in a stable, balanced, or unchanging system.

Nernst equation An equation used to calculate the equilibrium potential at a membrane.

	● Na^+	● K^+	● Cl^-	○ Ca^{2+}	● Proteins
Outside cell	many	few	many	many	few
Inside cell	few	many	few	few	many



3.4 The Distribution of Ions Inside and Outside of a Neuron Most potassium ions (K^+) are found inside the neuron; most sodium ions (Na^+) and chloride ions (Cl^-) are in the extracellular space. These ions are exchanged through specialized channels in the cell membrane. The large, negatively charged protein molecules stay inside the neuron and account for much of the negative resting potential.

to **sodium ions (Na^+)**. Small numbers of Na^+ ions leak in, drawn to the cell's negatively charged interior.

If left unchecked, this Na^+ leakage would eventually reduce the membrane potential to zero, and the cell would become incapable of generating electrical signals. But the neuron prevents this with a mechanism, the **sodium–potassium pump**, that pumps Na^+ out of the cell and K^+ in, just rapidly enough to counter the leakage (**Figure 3.3*b***). And because the pump evicts about 3 Na^+ ions for every 2 K^+ ions that it takes in, it actively maintains the negativity of the interior of the neuron. This action consumes energy because the pump is working against both the concentration gradient and electrostatic pressure. In fact, a large fraction of the energy consumed by the brain—whether waking or sleeping—is used to maintain the ionic differences across neuronal membranes. The distribution of ions is illustrated in **Figure 3.4**. Notice the high intracellular concentration of K^+ and the high extracellular concentration of Na^+.

The resting potential of a neuron provides a baseline level of polarization. What distinguishes neurons from most other cells is that they routinely undergo a brief but radical change in polarization, sending an electrical signal from one end of the neuron to the other, as we'll discuss next.

A threshold amount of depolarization triggers an action potential

Nerve impulses, or **action potentials**, are very brief but large changes in neuronal polarization that arise initially at the **axon hillock** (the specialized membrane located at the site where the axon emerges from the cell body; see Figure 2.7*a*), which are propagated at high speed along the axon. The information that a neuron sends to its postsynaptic targets is encoded in patterns of these action potentials, so we need to understand their properties—where they come from, how they race down the axon, and how they communicate their information across synapses to other cells. Let's turn first to the creation of the action potential.

Two concepts are central to understanding how action potentials are triggered. **Hyperpolarization** is an increase in membrane potential (i.e., the neuron becomes even more negative on the inside, relative to the outside). So if the neuron already has a resting membrane potential of, say, –60 mV, hyperpolarization makes it even *further from zero*, maybe –70 mV. **Depolarization** is the reverse, referring to a *decrease* in membrane

sodium ion (Na^+) A sodium atom that carries a positive charge because it has lost one electron.

sodium–potassium pump The energetically expensive mechanism that pushes sodium ions out of a cell, and potassium ions in.

action potential The propagated electrical message of a neuron that travels along the axon to the presynaptic axon terminals.

axon hillock A cone-shaped area from which the axon originates out of the cell body. Functionally, the integration zone of the neuron.

hyperpolarization An increase in membrane potential (the interior of the neuron becomes even more negative).

depolarization A reduction in membrane potential (the interior of the neuron becomes less negative).

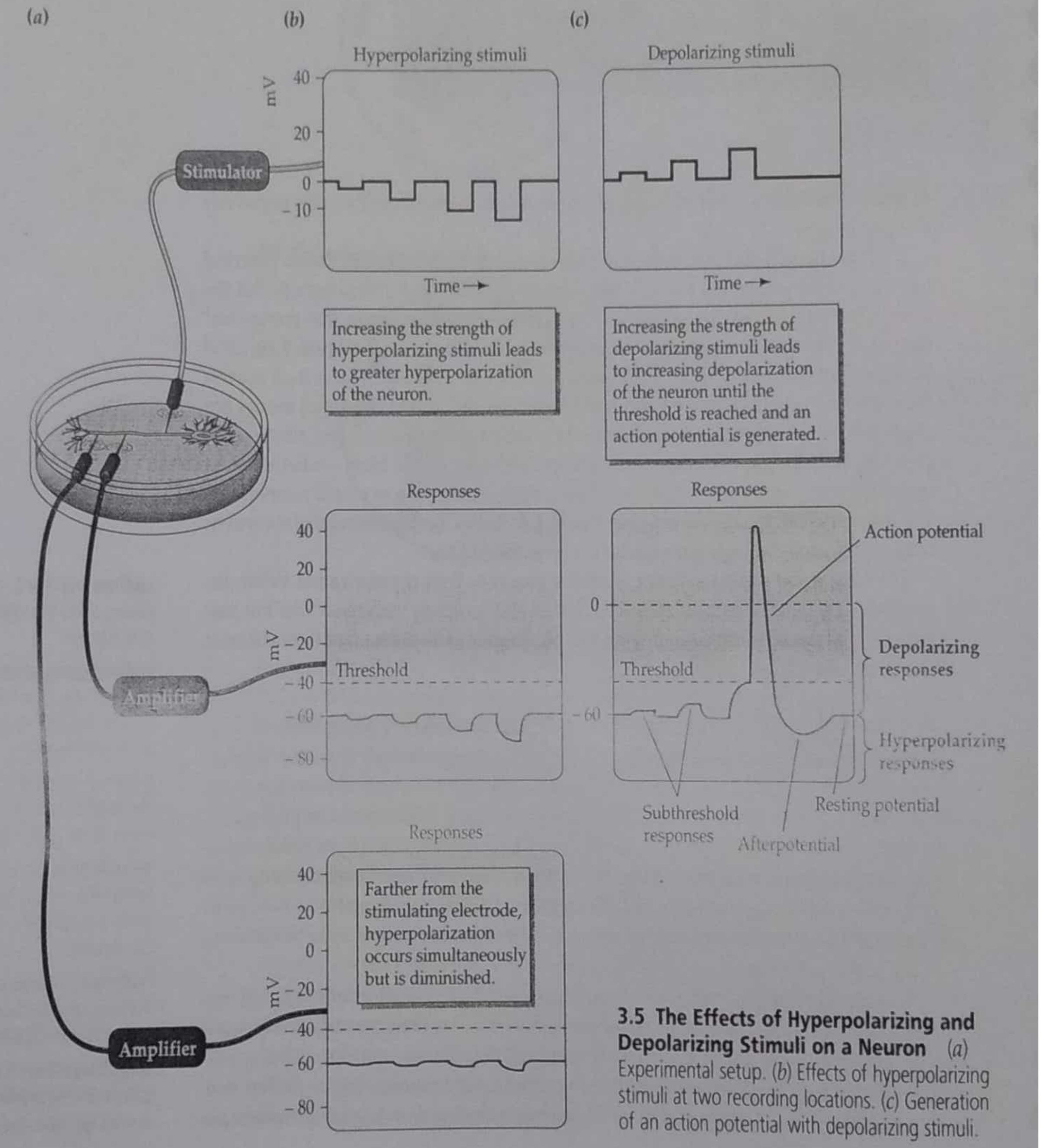
graded response A membrane electrical potential that spreads passively across the cell membrane, decreasing in strength with time and distance.

local potential An electrical potential that is initiated by stimulation at a specific site and spreads passively across the cell membrane, decreasing in strength with time and distance.

potential. The depolarization of a neuron from a resting potential of –60 mV to, say, –50 mV makes the inside of the neuron more like the outside. In other words, depolarization of a neuron brings its membrane potential *closer to zero.*

Figure 3.5a illustrates an apparatus for experimentally applying hyperpolarizing and depolarizing stimuli to a neuron, via electrodes. (Later we'll talk about how synapses from other neurons produce similar hyperpolarizations and depolarizations.) Applying a *hyperpolarizing* stimulus to the membrane produces an immediate response that passively follows the shape of the stimulus pulse (**Figure 3.5b**; the distortions at the beginning and end of the neuron's response are attributable to the membrane's ability to store electricity, known as *capacitance*). The greater the stimulus, the greater the response, so the neuron's change in potential is called a **graded response**.

[illegible]
[illegible]
response seems passive. Like the ripples spreading from a pebble dropped in a pond, the **local potentials** produced by stimulation of the membrane diminish as they spread


(a)
(b)
(c)
Hyperpolarizing stimuli
Depolarizing stimuli
mV
40
20
0
-10
Stimulator
Time →
Time →
Increasing the strength of hyperpolarizing stimuli leads to greater hyperpolarization of the neuron.
Increasing the strength of depolarizing stimuli leads to increasing depolarization of the neuron until the threshold is reached and an action potential is generated.
Responses
Responses
40
20
0
-20
-40
-60
-80
mV
Threshold
Amplifier
Threshold
Action potential
0
-60
Depolarizing responses
Hyperpolarizing responses
Resting potential
Subthreshold responses
Afterpotential
Responses
Farther from the stimulating electrode, hyperpolarization occurs simultaneously but is diminished.
40
20
0
-20
-40
-60
-80
mV
Amplifier

3.5 The Effects of Hyperpolarizing and Depolarizing Stimuli on a Neuron (*a*) Experimental setup. (*b*) Effects of hyperpolarizing stimuli at two recording locations. (*c*) Generation of an action potential with depolarizing stimuli.

away from the point of stimulation. A simple law of physics describes this phenomenon: as a local potential spreads across the membrane, its size decays as a function of the square of the distance.

Up to a point, the application of *depolarizing* pulses to the membrane follows the same pattern as for hyperpolarizing stimuli, producing local, graded responses. However, the situation changes suddenly if the stimulus depolarizes the cell to –40 mV or so (the exact value varies slightly among neurons). At this point, known as the **threshold**, a sudden and brief (0.5–2.0 ms) response—the action potential (**Figure 3.5c**), sometimes referred to as a *spike* because of its shape—is provoked. An action potential is a nearly instantaneous reversal of the membrane potential that momentarily makes the inside of the membrane *positive* with respect to the outside. Unlike the passive graded potentials that we have been discussing, the action potential is actively propagated (or regenerated) down the axon, through ionic mechanisms that we'll discuss shortly.

Applying strong stimuli to produce depolarizations that far exceed the neuron's threshold reveals another important property of action potentials: larger depolarizations do not produce larger action potentials. In other words, the size (or *amplitude*) of the action potential is independent of stimulus magnitude. This characteristic is referred to as the **all-or-none property** of the action potential: either it fires at its full amplitude, or it doesn't fire at all. It turns out that stimulus strength is encoded by changes in the *frequency* of action potentials rather than in their *amplitude*. With stronger stimuli, more action potentials are produced, but the size of each action potential remains the same.

A closer look at the form of the action potential shows that the return to baseline membrane potential is not simple. Many axons exhibit electrical oscillations immediately following the spike; these changes are called **afterpotentials** (see Figure 3.5c), and they are also related to the movement of ions in and out of the cell.

Ionic mechanisms underlie the action potential

What events explain the action potential? To answer this question, English neurophysiologists Alan Hodgkin (1914–1998) and Andrew Huxley (1917–) took advantage of the giant axon of the squid, part of a neuron involved in the animal's emergency escape behavior. At more than 500 μm in diameter, the giant axon of the squid is readily apparent to the naked eye, and therefore much better suited to experimentation than mammalian axons, which range in size from 0.5 to 20 μm in diameter. Microelectrodes can be inserted into a giant axon without greatly altering the properties or activity of the axon; it is even possible to push the intracellular fluid out of the squid axon and replace it with other fluids to study various properties of the action potential.

Experimental evidence revealed that the action potential is created by the movement of sodium ions (Na^+) into the cell, through the membrane (Hodgkin and Katz, 1949). At its peak, the action potential approaches the equilibrium potential for Na^+ as predicted by the Nernst equation: about +40 mV. At this point, the concentration gradient pushing Na^+ ions into the cell is exactly balanced by the positive charge pushing them out. The action potential thus involves a rapid shift in membrane properties, switching suddenly from the potassium-dependent resting state to a primarily sodium-dependent active state, and then swiftly returning to the resting state. How is this accomplished? Through the actions of a very special ion channel: the voltage-gated Na^+ channel.

Like other ion channels, the **voltage-gated Na^+ channel** is a tubular, membrane-spanning protein, but its central Na^+-selective pore is ordinarily closed. When the cell membrane becomes depolarized to threshold levels, however, the channel's shape changes and the Na^+ channel opens. Consider what happens when a patch of axonal membrane depolarizes (**Figure 3.6**). As the depolarization approaches threshold, some of these Na^+ channels open. As Na^+ ions start to enter the neuron, they reduce the membrane potential even further, causing still more Na^+ channels to open. Thus the process accelerates until the barriers are removed, and Na^+ ions rush in.

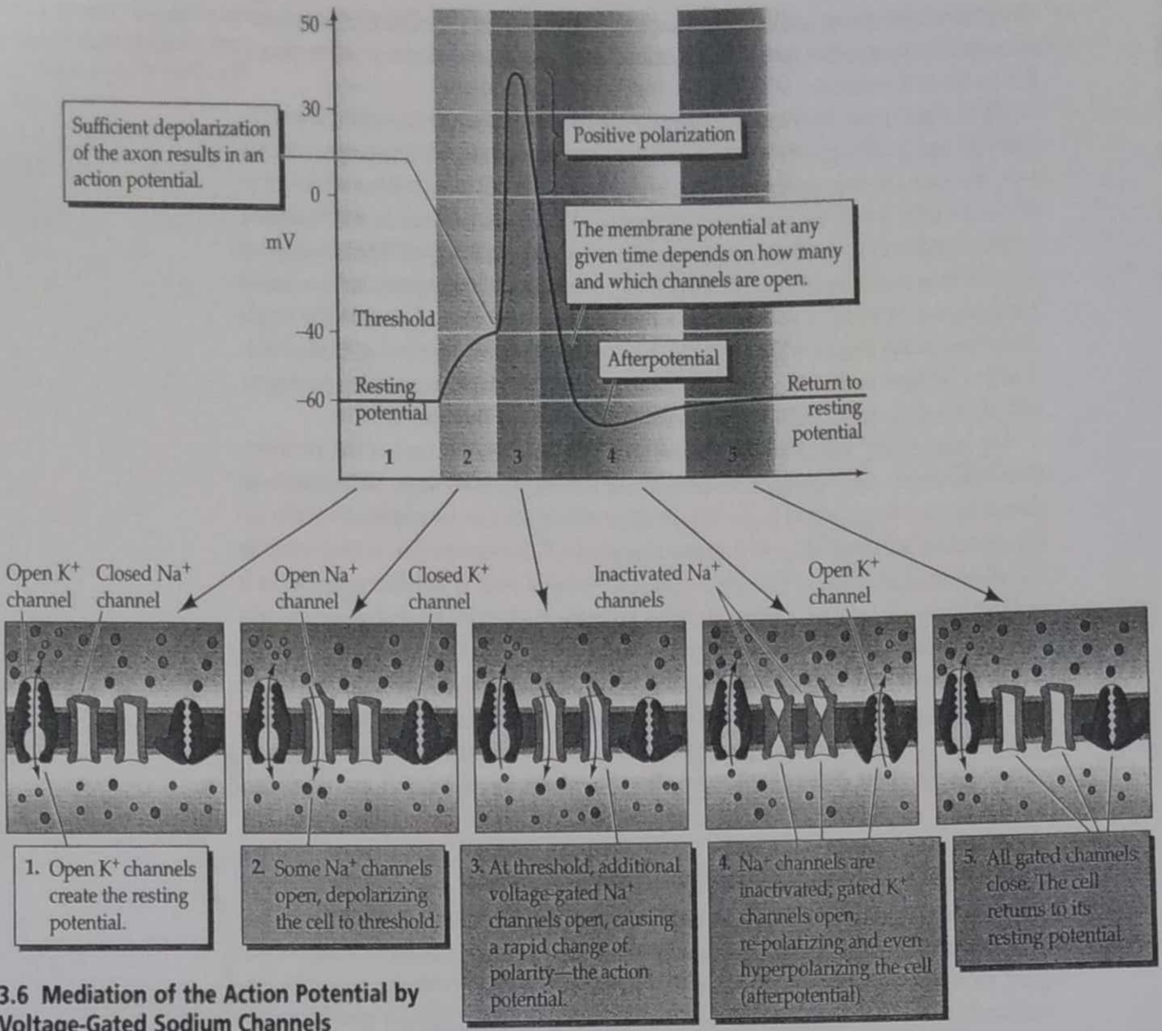
The voltage-gated Na^+ channels stay open for a little less than a millisecond; then they close again. By this time the membrane potential has reached the sodium equilib-

threshold The stimulus intensity that is just adequate to trigger a nerve impulse at the axon hillock.

all-or-none property The fact that the amplitude of the action potential is independent of the magnitude of the stimulus.

afterpotential The positive or negative change in membrane potential that may follow an action potential.

voltage-gated Na^+ channel An Na^+-selective channel that opens or closes in response to changes in the voltage of the local membrane potential; mediates the action potential.


50
30
0
mV
-40
-60
Sufficient depolarization of the axon results in an action potential.
Positive polarization
The membrane potential at any given time depends on how many and which channels are open.
Threshold
Afterpotential
Resting potential
Return to resting potential
1
2
3
4
5
Open K⁺ channel
Closed Na⁺ channel
Open Na⁺ channel
Closed K⁺ channel
Inactivated Na⁺ channels
Open K⁺ channel
1. Open K⁺ channels create the resting potential.
2. Some Na⁺ channels open, depolarizing the cell to threshold.
3. At threshold, additional voltage-gated Na⁺ channels open, causing a rapid change of polarity—the action potential.
4. Na⁺ channels are inactivated; gated K⁺ channels open, re-polarizing and even hyperpolarizing the cell (afterpotential).
5. All gated channels close. The cell returns to its resting potential.

3.6 Mediation of the Action Potential by Voltage-Gated Sodium Channels

rium potential of about +40 mV. Now positive charges inside the nerve cell tend to push K⁺ ions out, and voltage-gated K⁺ channels open, increasing the permeability to K⁺, so the resting potential is soon restored.

The application of very strong stimuli reveals another important property of axonal membranes. As we offer the beleaguered axon ever-greater stimuli, an upper limit to the frequency of action potentials becomes apparent at about 1200 spikes per second. (Many neurons have even slower maximum rates of response.) Similarly, applying pairs of stimuli that are spaced closer and closer together reveals a related phenomenon: beyond a certain point, only the first stimulus is able to elicit an action potential. The axonal membrane is said to be **refractory** (unresponsive) to the second stimulus.

Refractoriness has two phases: During the **absolute refractory phase**, a brief period immediately following the production of an action potential, no amount of stimulation can induce another action potential, because the voltage-gated Na⁺ channels are either still open or unresponsive. The absolute phase is followed by a period of reduced sensitivity, the **relative refractory phase**, during which only a very strong stimulation can produce another action potential because K⁺ ions are still flowing and because the cell is temporarily hyperpolarized after firing an action potential (see Figure 3.6). The overall length of the refractory phase is what determines a neuron's maximal rate of firing.

This tiny protein molecule, the voltage-gated Na⁺ channel, is thus quite a complicated machine. It monitors the axon's polarity, and at threshold the channel changes its shape to open the pore, shutting down again just a millisecond later. The channel then "remembers" that it was open lately and refuses to open again for a short time. These

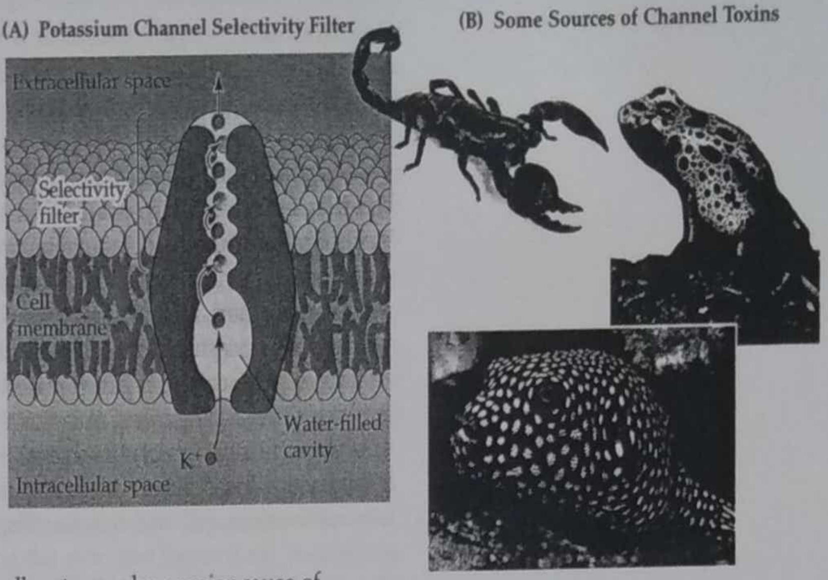
refractory Transiently inactivated or exhausted.

absolute refractory phase A brief period of complete insensitivity to stimuli.

relative refractory phase A period of reduced sensitivity during which only strong stimulation produces an action potential.

properties produce and enforce the properties of the action potential. As you might expect, anything that alters the functioning of neuronal ion channels can have dire consequences (**Box 3.1**).

BOX 3.1 Changing the Channel



The cell membrane is made up of fatty molecules, so it tends to repel water. Because ions in body fluids are usually surrounded by clusters of water molecules, they cannot easily pass directly through neuronal membranes. Instead, they must pass through membrane-spanning ion channels, which are highly selective for particular types of ions. Recent research has begun to reveal some of the functional details of these channels, such as the K^+ channel shown in Figure A (Berneche and Roux, 2001; Morais-Cabral et al., 2001; Zhou et al., 2001). The inner surfaces of the K^+ channel are lined with oxygen atoms that mimic water molecules. With the oxygen atoms substituting for their usual escort of water molecules, K^+ ions fit exactly into this *selectivity filter*. Other ions, such as the smaller Na^+ ions, do not fit as comfortably and thus remain outside, in solution. The end result is a 10,000-fold selectivity for K^+ ions!

Given the extreme precision with which these ion channels must operate, it's no surprise that even the most minor alteration of channel functioning causes people serious health problems (Kass, 2005). A **channelopathy** is a medical condition in which the form and function of ion channels is altered as a result of mutation of the genes that encode them. Sodium channelopathy—a problem with sodium channels—is associated with a variety of seizure disorders, as well as heritable muscle diseases and certain types of cardiac ailments (S. C. Cannon, 1996; George, 2005; Kass, 2005). Chloride channel disorders can result in deafness, kidney problems, and neuromuscular disorders (T. J. Jentsch et al., 2005), as well as seizures. In fact, evidence is mounting that mutations in ion channel genes of all sorts may be a major cause of epilepsy (Steinlein, 2004).

The critical importance of channels is also exploited by a variety of potent animal toxins (Figure B). For example, **tetrodotoxin** (**TTX**) and **saxitoxin** (**STX**) selectively block voltage-gated sodium channels, thereby preventing the production of action potentials; paralysis and death rapidly follow. Tetrodotoxin is found in the ovaries of the puffer fish, which is esteemed as a delicacy in Japan. If the ovaries of the puffer fish are not removed properly and if the fish is not cleaned with great care, people who eat it may be poisoned by TTX. Saxitoxin is likewise a seafood threat: it derives from "red tide," a bloom of algae that sometimes affects shellfish. The extremely potent neurotoxin **batrachotoxin**, produced by South American poison arrow frogs, has the reverse effect and forces Na^+ channels to stay open, with equally lethal results. Scorpions are a rich source of channel-specific toxins; some species produce toxins that specifically block Na^+ channels, while others target K^+ channels.

Tiny quantities of any of these toxins can dramatically impede the ability of neurons to function. However, the same specificity that makes channel toxins so deadly also makes them useful tools in the laboratory. For example, the venom of the tarantula spider contains toxins that very specifically target the voltage sensor of certain voltage-gated ion channels; in the lab, these toxins have provided important clues about how such channels work (S.-Y. Lee and MacKinnon, 2004). The use of channel-selective toxins and other experimental techniques for studying ion channels is discussed on the website in **A Step Further: How Can We Study Ion Channels?**

channelopathy A genetic abnormality of ion channels, causing a variety of symptoms.

tetrodotoxin (TTX) A toxin from puffer fish ovaries that blocks the voltage-gated sodium channel, preventing action potential conduction.

saxitoxin (STX) An animal toxin that blocks sodium channels when applied to the outer surface of the cell membrane.

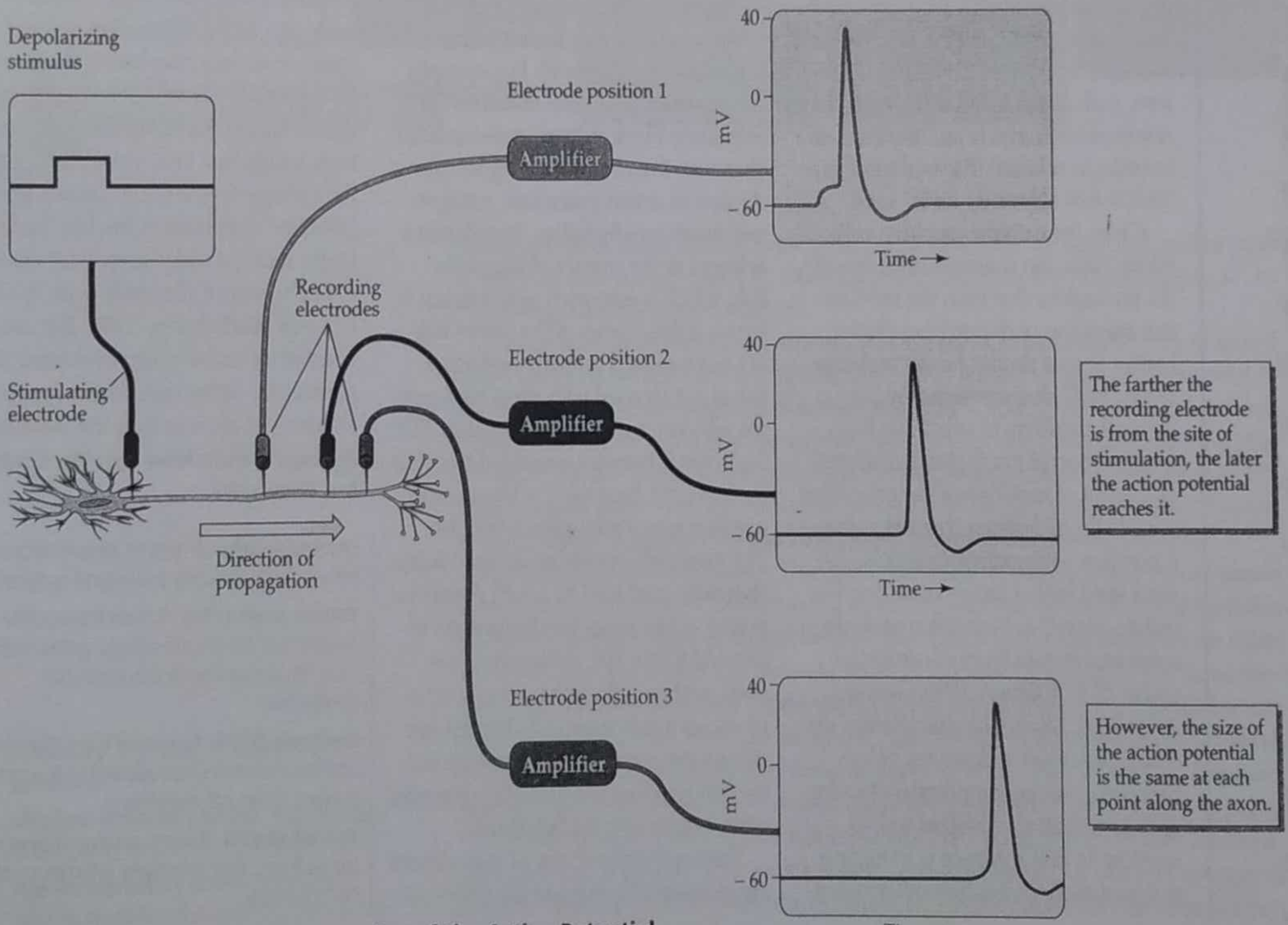
batrachotoxin A toxin, produced by poison arrow frogs, that selectively interferes with Na^+ channels.

In general, the transmission of action potentials is limited to axons. Because of the kinds of membrane channels they contain, cell bodies and most dendrites do not conduct action potentials. The cell body and dendrites have ion channels that are gated by certain chemicals, and they can therefore be stimulated chemically, as we'll discuss later in this chapter. But cell bodies and dendrites usually have few voltage-gated Na^+ channels. Because the axon has many such channels, once an action potential starts at the axon hillock, it regenerates itself down the length of the axon, as we discuss next.

Action potentials are actively propagated along the axon

Now that we have explored how voltage-gated channels contribute to the creation of action potentials, we can turn to the question of how action potentials are transmitted down the axon—because voltage-gated channels are crucial for this function too. Consider an experimental setup like the one pictured in **Figure 3.7**: recording electrodes are positioned along the length of the axon, allowing us to record an action potential at successive positions as it races toward the axon terminals. Recordings from this apparatus would show that an action potential initiated near the cell body spreads in a sort of chain reaction along the length of the axon, traveling at speeds that range from less than 1 meter per second (m/s) in some axons to more than 100 m/s in others.

How does the action potential travel? It is important to understand that the action potential is *regenerated* along the length of the axon. Remember, the action potential is a spike of depolarizing electrical activity (with a peak of about +40 mV), so it strongly depolarizes the next adjacent axon segment. Because this adjacent segment is similarly covered with voltage-gated Na^+ channels, the depolarization immediately creates a new action potential, which in turn depolarizes the next patch of membrane, which gener-



The farther the recording electrode is from the site of stimulation, the later the action potential reaches it.

However, the size of the action potential is the same at each point along the axon.

3.7 Propagation of the Action Potential

ates yet another action potential, and so on all down the length of the axon. An analogy is the spread of fire along a row of closely spaced match heads in a matchbook. When one match is lit, its heat is enough to ignite the next match and so on along the row. Voltage-gated Na^+ channels open when the axon is depolarized to threshold. In turn, the influx of Na^+ ions—the movement into the cell of positive charges—depolarizes the adjacent segment of axonal membrane and therefore opens new gates for the movement of Na^+ ions.

The axon normally conducts action potentials in only one direction—from the axon hillock toward the axon terminals—because as it progresses along the axon, the action potential leaves in its wake a stretch of refractory membrane (**Figure 3.8*a***). Propagated activity does not spread from the axon hillock back over the cell body and dendrites, because the membrane there does not possess voltage-gated Na^+ channels, so it cannot produce a regenerated action potential.

If we record the speed of action potentials along axons that differ in diameter, we see that **conduction velocity** varies with the diameter of the axon. Larger axons allow the depolarization to spread faster through the interior. In mammals, relatively large, heavily myelinated fibers are found in sensory and motor nerves. In these neurons, conduction velocity may be as fast as 120 m/s. (We discuss axon diameter and conduction velocity again in Chapter 8.) Although not as fast as the speed of light, as it was once believed to be, neural conduction is nevertheless very fast: up to about one-third the speed of sound in air. This relatively high rate of conduction ensures rapid sensory and motor processing.

The myelin sheathing on larger mammalian nerve fibers greatly speeds conduction. As we described in Chapter 2, the myelin sheath is interrupted by **nodes of Ranvier**, small gaps spaced about every millimeter along the axon (see Figure 2.6*b*). Because the myelin insulation offers considerable resistance to the flow of ionic currents across the membrane, the action potential jumps from node to node. This process is called **saltatory conduction** (from the Latin *saltare*, "to leap or jump") (**Figure 3.8*b***). The evolution of rapid saltatory conduction in vertebrates has given them a major behavioral advantage over invertebrates, in which axons are unmyelinated and mostly small in diameter, and thus slower in conduction.

To address this problem, many invertebrates have a few giant axons, which mediate essential motor responses, such as escape behavior. Remember that the larger the axon, the faster the conduction velocity. The giant axon of the squid has an unusually high conduction rate for an invertebrate, but it is still only about 20 m/s, much slower than myelinated axons (despite their smaller size).

To conduct action potentials as swiftly as a myelinated vertebrate axon does, an unmyelinated invertebrate axon would have to be 100 times larger in volume. It has been estimated that at least 10% of the volume of the human brain is occupied by myelinated axons. To maintain the conduction velocity of our cerebral neurons without the help of myelin, our brains would have to be ten times as large as they are. This helps explain why myelination is an important index of maturation of the developing nervous system (see Chapter 7).

The function of synapses is to cause local changes in the postsynaptic membrane potential

At the beginning of the chapter, we related the tale of Otto Loewi's discovery of chemical signaling between neurons. Through painstaking experimentation, Loewi eventually proved that the chemical inhibiting the heart (which he called *Vagusstoff*) was actually acetylcholine. Acetylcholine was thus the first demonstrated **neurotransmitter** (or **transmitter**), a chemical released by a neuron to affect a postsynaptic cell. We will discuss transmitters later in this chapter and in Chapter 4. Although many synapses use a chemical signal such as acetylcholine, eventually it was found that the nervous system also employs electrical synapses (**Box 3.2**).

What all neurotransmitters have in common is that they briefly alter the resting potential of the postsynaptic cell. We call these brief changes **postsynaptic potentials**. A

conduction velocity The speed at which an action potential is propagated along the length of an axon (or section of peripheral nerve).

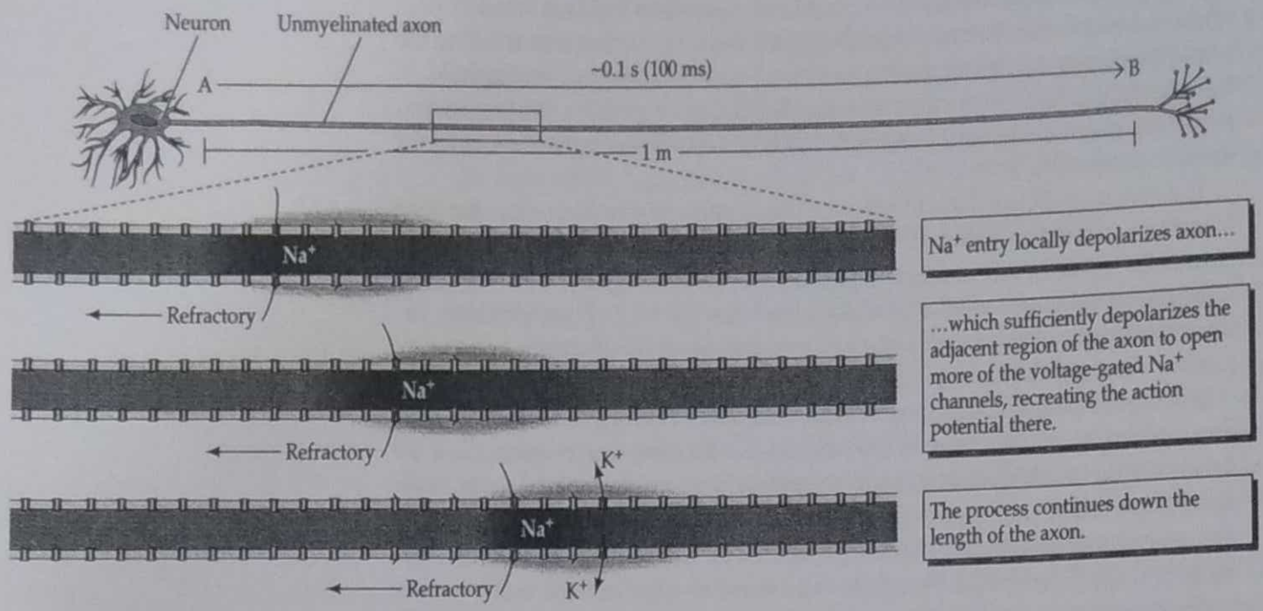
node of Ranvier A gap between successive segments of the myelin sheath where the axon membrane is exposed.

saltatory conduction The form of conduction that is characteristic of myelinated axons, in which the nerve impulse jumps from one node of Ranvier to the next.

neurotransmitter Also simply called *transmitter*. The chemical, released from the presynaptic axon terminal, that serves as the basis of communication between neurons.

postsynaptic potential Also called *graded potential* or *local potential*. An electrical potential that is initiated at a postsynaptic site that can vary in amplitude and spreads passively across the cell membrane, decreasing in strength with time and distance.

(*a*) **Slow (10 m/s) conduction of action potential along unmyelinated axon**

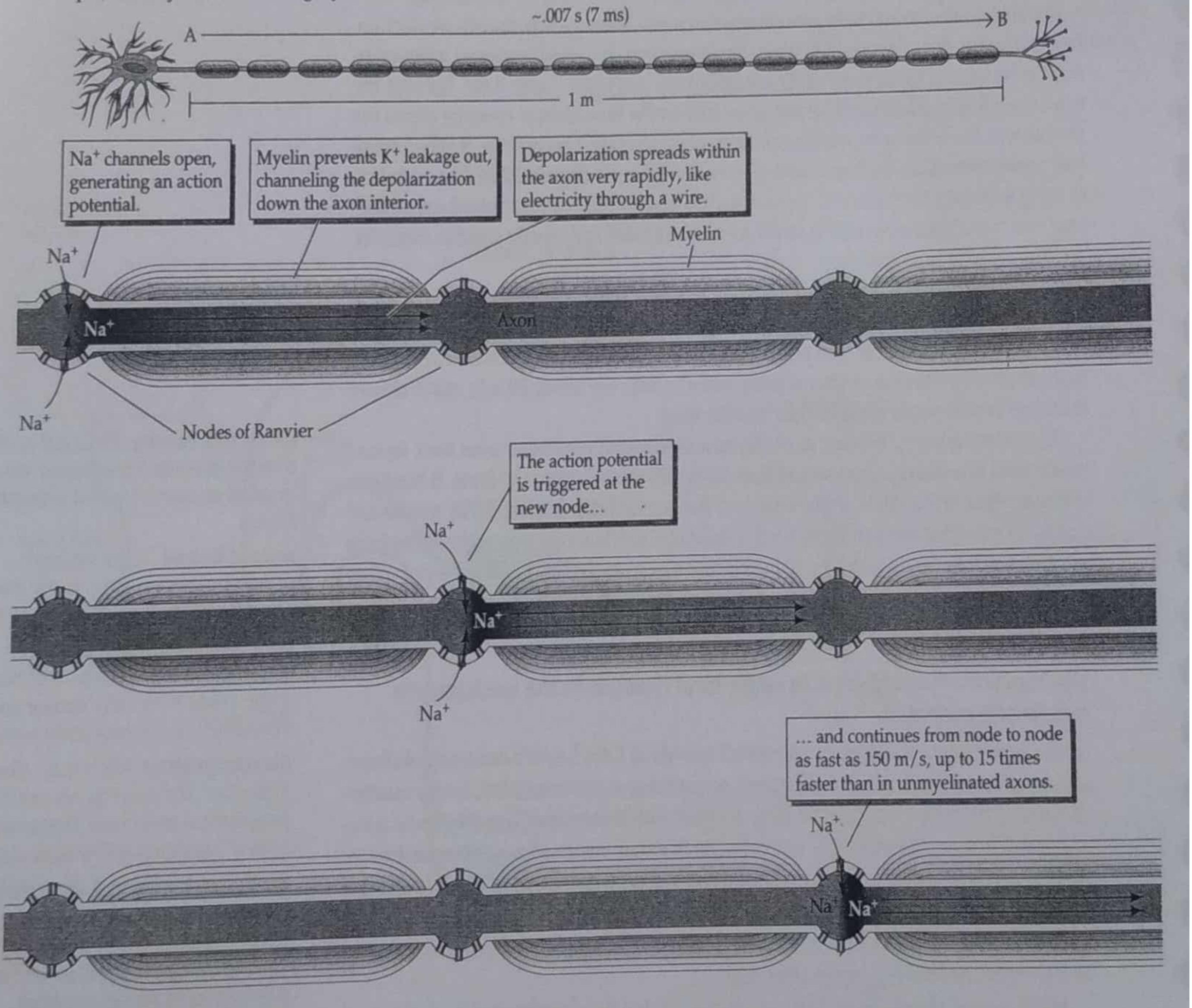

Neuron
Unmyelinated axon
A
~0.1 s (100 ms)
B
1 m
Na+
Refractory
Na+
Refractory
K+
Na+
Refractory
K+

Na⁺ entry locally depolarizes axon...

...which sufficiently depolarizes the adjacent region of the axon to open more of the voltage-gated Na⁺ channels, recreating the action potential there.

The process continues down the length of the axon.

(*b*) **Rapid, saltatory conduction along myelinated axon**


A
~.007 s (7 ms)
B
1 m
Myelin
Na+
Na+
Axon
Na+
Nodes of Ranvier
Na+
Na+
Na+
Na+
Na+
Na+

Na⁺ channels open, generating an action potential.

Myelin prevents K⁺ leakage out, channeling the depolarization down the axon interior.

Depolarization spreads within the axon very rapidly, like electricity through a wire.

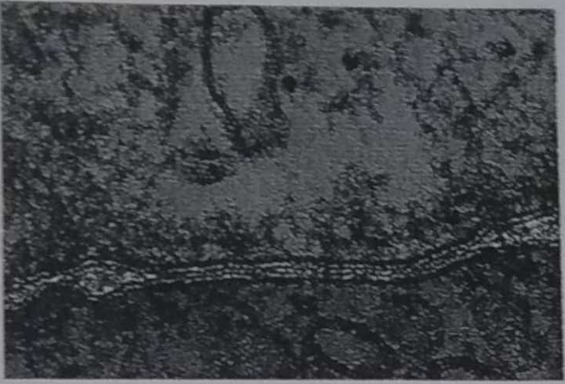
The action potential is triggered at the new node...

... and continues from node to node as fast as 150 m/s, up to 15 times faster than in unmyelinated axons.

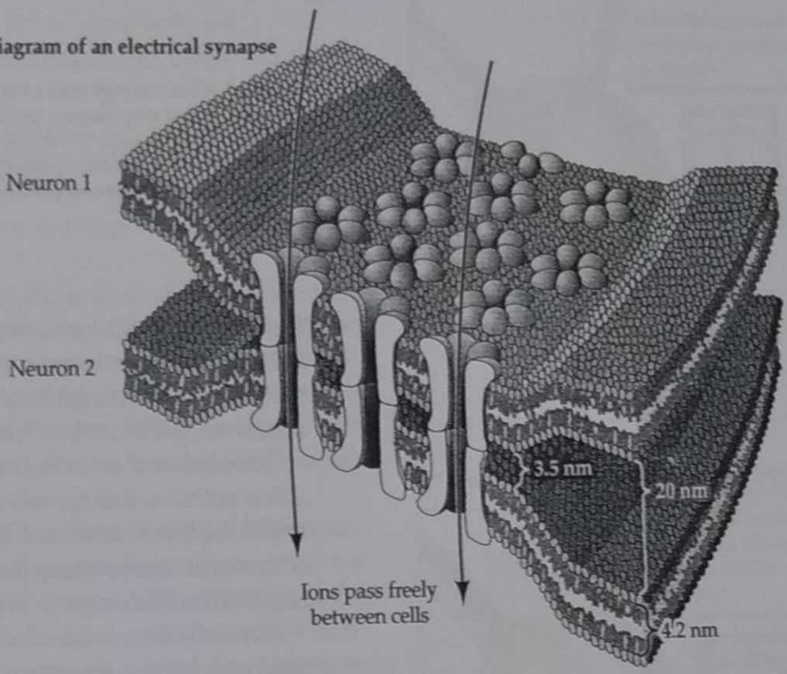
3.8 Conduction along Unmyelinated versus Myelinated Axons

BOX 3.2 Electrical Synapses Work with No Time Delay

(A) Electron micrograph of an electrical synapse



(B) Diagram of an electrical synapse



Although we are focusing on synapses that require a chemical substance to mediate synaptic transmission, electrical synapses are also widespread in the brain (M.V. Bennett, 2000). At **electrical synapses** (or **gap junctions**) the presynaptic membrane comes even closer to the postsynaptic membrane than it does at chemical synapses; the gap at an electrical synapse (Figure A) measures only 2 to 4 nm. In contrast, the synaptic cleft of a chemical synapse is 20 to 40 nm. At electrical synapses, the facing membranes of the two cells have relatively large channels arranged to allow ions to flow from one neuron directly into the other (Figure B). As a consequence, the flow of electrical current that is associated with neural activity in the presynaptic cell can travel directly across the presynaptic and the postsynaptic membranes.

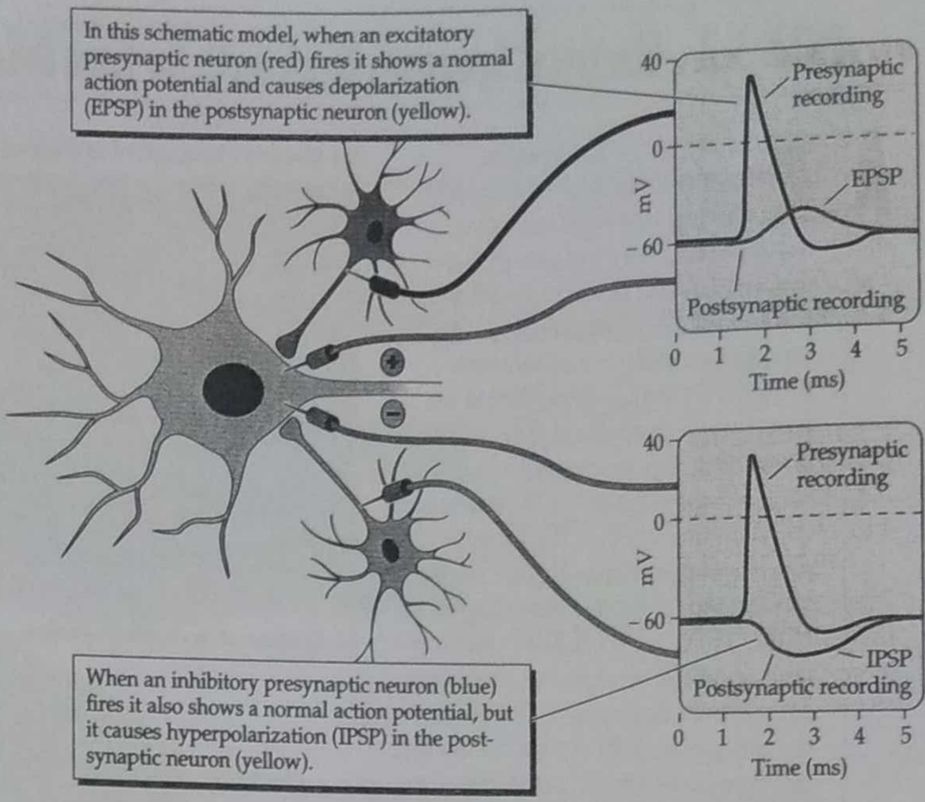
Transmission at these synapses closely resembles conduction along the axon. Electrical synapses therefore work with practically no time delay, in contrast to chemical synapses, where the delay is on the order of a millisecond—slow in terms of neurons. Because of the speed of their transmission, electrical synapses are frequently found in neural circuits that mediate escape behaviors in invertebrates. They are also found where many fibers must be activated synchronously, as in the system for moving our eyes; and they are widely found in mammalian thalamus and cortex, particularly between inhibitory neurons (Gibson et al., 1999). As with chemical synapses, the potency of gap junctions can change in response to changes in activity in the brain (Landisman and Connors, 2005), perhaps contributing to memory formation. Clinically, it is suspected that electrical synapses contribute to the spread of synchronized seizure discharges in epilepsy (Szente et al., 2002). (Figure A courtesy of Constantino Sotelo.)

electrical synapse Also called *gap junction*. The region between neurons where the presynaptic and postsynaptic membranes are so close that the nerve impulse can jump to the postsynaptic membrane without first being translated into a chemical message.

given neuron, receiving synapses from hundreds of other cells, is subject to hundreds or thousands of postsynaptic potentials. When integrated, this massive array of local potentials determines whether the neuron will reach threshold and therefore generate an action potential of its own.

We can study postsynaptic potentials with a setup like that shown in **Figure 3.9**. This setup allows us to compare the effects of activity of excitatory (red) versus inhibitory (blue) presynaptic cells on the local membrane potential of a postsynaptic cell (yellow).

3.9 Recording Postsynaptic Potentials



In this schematic model, when an excitatory presynaptic neuron (red) fires it shows a normal action potential and causes depolarization (EPSP) in the postsynaptic neuron (yellow).

When an inhibitory presynaptic neuron (blue) fires it also shows a normal action potential, but it causes hyperpolarization (IPSP) in the postsynaptic neuron (yellow).

The responses of the presynaptic and postsynaptic cells are shown on the same graphs in Figure 3.9 for easy comparison of their time relations. It is important to remember that excitatory and inhibitory neurons get their names from their actions on *postsynaptic neurons*, not from their effects on *behavior*.

Stimulation of an excitatory presynaptic neuron causes it to produce an all-or-none action potential that spreads to the end of the axon. After a brief delay, the postsynaptic cell displays a small local depolarization. This postsynaptic membrane depolarization is known as an **excitatory postsynaptic potential** (**EPSP**) because it pushes the postsynaptic cell a little closer to the threshold for an action potential.

Generally the combined effect of many excitatory synapses is required to elicit an action potential in a postsynaptic neuron. If EPSPs are elicited almost simultaneously by many neurons that converge on the postsynaptic cell, these potentials can sum and produce a depolarization large enough to reach threshold and trigger an action potential. Note that there is a delay: in the fastest cases, the postsynaptic depolarization begins about half a millisecond after the presynaptic action potentials arrive at the axon terminals. This **synaptic delay** reflects the time needed for the neurotransmitter to be released and diffuse across the synaptic cleft, as we'll discuss later.

The action potential of an inhibitory presynaptic neuron looks exactly like that of the excitatory presynaptic neuron; all neurons use the same kind of propagated signal (see Figure 3.9). But the effect on the *postsynaptic* side is quite different. When the inhibitory neuron is stimulated, the postsynaptic effect is an *increase* of the resting membrane potential. This hyperpolarization moves the cell membrane potential away from threshold—it *decreases* the probability that the neuron will fire an action potential—so it is called an **inhibitory postsynaptic potential** (**IPSP**).

Usually IPSPs result from the opening of channels that permit **chloride ions** (**Cl^-**) to enter the cell. Because Cl^- ions are much more concentrated outside the cell than inside (see Figure 3.4), they rush into the cell, making it even more negative. Although in this discussion we have been paying more attention to excitation, inhibition also plays a vital role in the neural processing of information. Just as driving a car requires brakes as well as an accelerator, neural switches must be turned off as well as on. The nervous sys-

excitatory postsynaptic potential (EPSP) A depolarizing potential in the postsynaptic neuron that is caused by excitatory presynaptic impulses. EPSPs increase the probability that the postsynaptic neuron will fire an action potential.

synaptic delay The brief delay between the arrival of an action potential at the axon terminal and the creation of a postsynaptic potential.

inhibitory postsynaptic potential (IPSP) A hyperpolarizing potential in the postsynaptic neuron that is caused by inhibitory connections. IPSPs decrease the probability that the postsynaptic neuron will fire an action potential.

chloride ion (Cl^-) A chlorine atom that carries a negative charge because it has gained one electron.

tem treads a narrow path between overexcitation, which leads to seizures (see Box 3.3), and underexcitation which leads to coma and death.

What determines whether a synapse excites or inhibits the postsynaptic cell? One factor is the particular neurotransmitter released by the presynaptic cell. Some transmitters generate an EPSP in the postsynaptic cells; others generate an IPSP. Whether a neuron fires an action potential at any given moment is decided by the balance between the number of excitatory and the number of inhibitory signals that it is receiving, and it receives many signals of both types at all times.

Spatial summation and temporal summation integrate synaptic inputs

Synaptic transmission is an impressive process, but complex behavior requires more than the simple conveyance of nerve signals across synapses. Neurons must also be able to integrate and transform the messages that they receive. In other words, they perform *information processing*. This is accomplished by a sort of neural algebra, in which each nerve cell adds and subtracts the myriad inputs it receives from other neurons. As we'll see next, these operations are possible because of the characteristics of synaptic inputs, the way in which the neuron integrates the postsynaptic potentials, and the trigger mechanism that determines whether a neuron will fire an action potential.

As we have seen, the postsynaptic potentials that are caused by transmitter chemicals can be either depolarizing (excitatory) or hyperpolarizing (inhibitory). From their points of origin on the dendrites and cell body, these EPSPs and IPSPs spread passively over the neuron, decreasing in strength over time and distance. Whether the postsynaptic neuron will fire an action potential is determined by whether a depolarization exceeding threshold reaches the axon hillock, the trigger zone in mammalian neurons.

The conceptual model in **Figure 3.10** illustrates the process of information processing by a neuron. For simplicity, no dendrites are shown, and all inputs synapse on the cell body. The presynaptic terminals are represented as simple electrical contacts through which excitatory (depolarizing) or inhibitory (hyperpolarizing) current may be applied to the postsynaptic cell membrane. The axon hillock contains a voltmeter; if the membrane potential rises (depolarizes) above a threshold level, an action potential is fired.

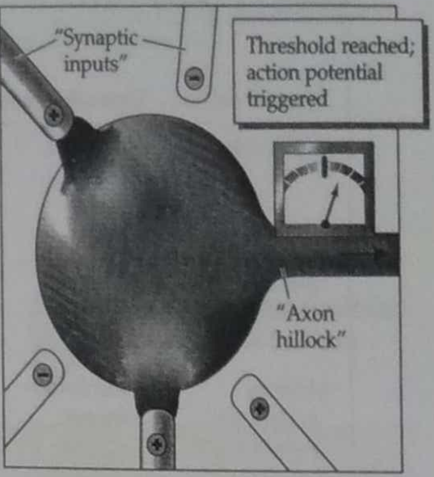
Suppose that two excitatory endings are activated, as shown in **Figure 3.10*a***, causing local depolarizations (in red) of the cell body. These depolarizations spread out over the neuron, dissipating as they spread, so that only a small proportion of the original depolarization reaches the axon hillock. Taken alone, neither would be sufficient to reach threshold depolarization, but when combined, the two depolarizations sum to push the hillock region to threshold.

Figure 3.10*b* shows what happens when inhibitory synapses also are active, creating postsynaptic hyperpolarizations. These hyperpolarizations also spread passively, dissipating as they travel. Because some potentials excite and others inhibit the hillock, these effects partially cancel each other. Thus the net effect is the difference between the two: the neuron subtracts the IPSPs from the EPSPs. Simple arithmetic, right?

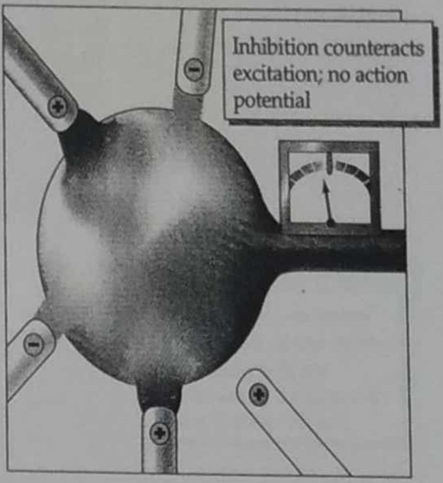
When summed, EPSPs and IPSPs do tend to cancel each other out. But because postsynaptic potentials spread passively and dissipate as they cross the cell membrane, the resulting sum is also influenced by distance. For example, simultaneous EPSPs from two synapses close to the hillock will produce a larger sum there than will two EPSPs from farther away. The summation of potentials originating from different physical locations across the cell body is called **spatial summation**. Only if the overall sum of *all* the potentials—both EPSPs and IPSPs—is sufficient to depolarize the cell to threshold at the axon hillock, is an action potential triggered (**Figure 3.10*c***). Usually the convergence of excitatory messages from many presynaptic neurons (and not a lot of inhibitory inputs) is required for a neuron to fire an action potential.

Postsynaptic effects that are not absolutely simultaneous can also be summed, because the postsynaptic potentials last a few milliseconds before fading away. The closer they are in time, the greater is the overlap and the more complete is the summation,

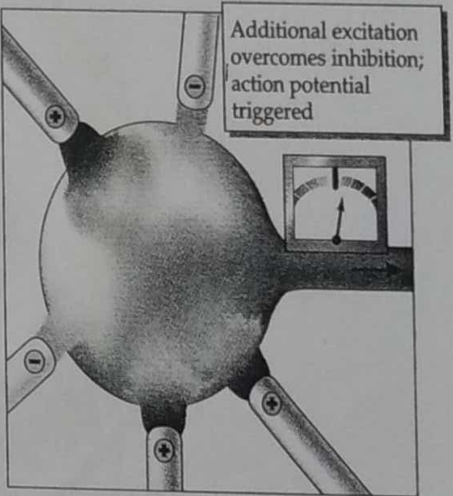
(*a*) Excitatory inputs cause the cell to fire



(*b*) Inhibition also plays a role



(*c*) The cell integrates excitation and inhibition


Additional excitation overcomes inhibition; action potential triggered

3.10 Spatial Summation in a Postsynaptic Cell

spatial summation The summation at the axon hillock of postsynaptic potentials from across the cell body. If this summation reaches threshold, an action potential is triggered.

TABLE 3.1 Characteristics of Electrical Signals of Nerve Cells

Type of signal	Signaling role	Typical duration (ms)	Amplitude	Character	Mode of propagation	Ion channel opening	Channel sensitive to:
Action potential	Conduction along a neuron	1–2	Overshooting, 100 mV	All-or-none, digital	Actively propagated, regenerative	First Na⁺, then K⁺, in different channels	Voltage (depolarization)
Excitatory postsynaptic potential (EPSP)	Transmission between neurons	10–100	Depolarizing, from less than 1 to more than 20 mV	Graded, analog	Local, passive spread	Na⁺–K⁺	Chemical (neurotransmitter)
Inhibitory postsynaptic potential (IPSP)	Transmission between neurons	10–100	Hyperpolarizing, from less than 1 to about 15 mV	Graded, analog	Local, passive spread	K⁺–Cl⁻	Chemical (neurotransmitter)

which in this case is called **temporal summation**. Temporal summation is easily understood if you imagine a neuron with only one input. If EPSPs arrive one right after the other, they sum and the postsynaptic cell eventually reaches threshold and produces an action potential. If too much time passes between EPSPs, the neuron will never fire.

It should now be clear that, although nerve impulses are all-or-none phenomena, the overall postsynaptic effect is graded in size and determined by the processing of numerous inputs occurring close together in time. The membrane potential at the axon hillock thus reflects the moment-to-moment integration of all of its inputs, which the hillock encodes into an ongoing pattern of action potentials.

Dendrites have been omitted from Figure 3.10 for simplicity, but they add to the story. In reality, a vast number of synaptic inputs, arrayed across the dendrites and cell body, can induce postsynaptic potentials. Dendrites therefore augment the receptive surface of the neuron and increase the amount of input information that the neuron can handle. We've already mentioned that proximity is an important factor in the summation of EPSPs and IPSPs. All other things being equal, therefore, the farther out on a dendrite that a potential is produced, the less effect the potential should have at the axon hillock, because the potential decreases in amplitude (i.e., strength) as it passively spreads. When the potential arises at a dendritic spine, its effect is further reduced because it has to spread down the shaft of the spine. Thus, information arriving at various parts of the neuron is weighted in terms of the distance and path resistance to the axon hillock.

Interestingly, in some types of neurons, synapses that are distant from the axon hillock compensate by producing larger local potentials. These large local potentials boost the effectiveness of the more distant synapses on the integration process occurring at the axon hillock, making the more distant synapses more comparable to nearer synapses. Furthermore, some neurons have *dendritic* integration zones, featuring voltage-gated ion channels, which sum and amplify local postsynaptic potentials, increasing their eventual impact at the axon hillock (S. R. Williams and Stuart, 2003). And finally, glial cells also play a role in synaptic transmission: they increase the strength of the postsynaptic potential (Pfrieger and Barres, 1997), overlying the presynaptic terminal and thereby preventing neurotransmitter leakage out of the synaptic cleft.

Table 3.1 summarizes the many properties of action potentials, EPSPs, and IPSPs, noting the principal similarities and differences among the three kinds of neural potentials.

temporal summation The summation of postsynaptic potentials that reach the axon hillock at different times. The closer in time that the potentials occur, the more complete the summation.

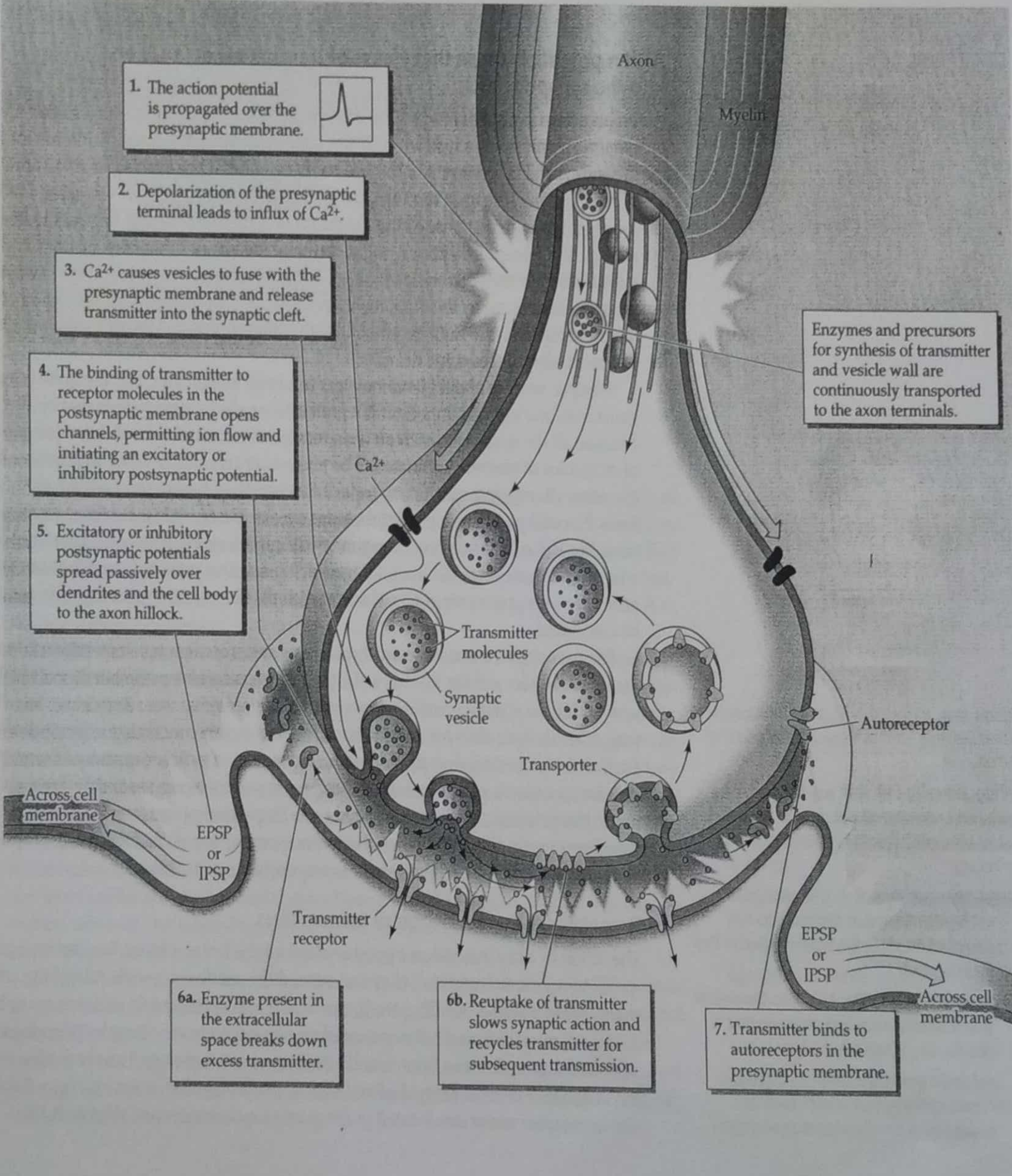
The Sequence of Transmission Processes at Chemical Synapses

The sequence of events during chemical synaptic transmission, shown in **Figure 3.11**, includes the following main steps:

1. The action potential is propagated into the presynaptic axon terminal.
2. Voltage-gated calcium channels in the membrane of the axon terminal open, and **calcium ions** (Ca^{2+}) enter the axon terminal.
3. Ca^{2+} causes synaptic vesicles, filled with neurotransmitter, to fuse with the presynaptic membrane and rupture, releasing the transmitter molecules into the synaptic cleft.

calcium ion (Ca^{2+}) A calcium atom that carries a double positive charge because it has lost two electrons.

3.11 Steps in Transmission at a Chemical Synapse


Axon
Myelin
1. The action potential is propagated over the presynaptic membrane.
2. Depolarization of the presynaptic terminal leads to influx of Ca2+.
3. Ca2+ causes vesicles to fuse with the presynaptic membrane and release transmitter into the synaptic cleft.
4. The binding of transmitter to receptor molecules in the postsynaptic membrane opens channels, permitting ion flow and initiating an excitatory or inhibitory postsynaptic potential.
5. Excitatory or inhibitory postsynaptic potentials spread passively over dendrites and the cell body to the axon hillock.
Enzymes and precursors for synthesis of transmitter and vesicle wall are continuously transported to the axon terminals.
Ca2+
Transmitter molecules
Synaptic vesicle
Autoreceptor
Transporter
Across cell membrane
EPSP or IPSP
Transmitter receptor
EPSP or IPSP
Across cell membrane
6a. Enzyme present in the extracellular space breaks down excess transmitter.
6b. Reuptake of transmitter slows synaptic action and recycles transmitter for subsequent transmission.
7. Transmitter binds to autoreceptors in the presynaptic membrane.

4. Some transmitter molecules bind to special receptor molecules in the postsynaptic membrane, leading—directly or indirectly—to the opening of ion channels in the postsynaptic membrane. The resulting flow of ions creates a local EPSP or IPSP in the postsynaptic neuron.
5. The IPSPs and EPSPs in the postsynaptic cell spread toward the axon hillock, interacting with each other along the way. If the integration of all the EPSPs and IPSPs ultimately results in a depolarization sufficient to reach threshold, the neuron will fire an action potential.
6. Then synaptic transmitter is either (a) inactivated (degraded) by enzymes; or (b) removed rapidly from the synaptic cleft by transporters, so the transmission is brief and accurately reflects the activity of the presynaptic cell.
7. Synaptic transmitter may also activate presynaptic *autoreceptors*, resulting in a decrease in transmitter release.

Action potentials cause the release of transmitter molecules into the synaptic cleft

When an action potential reaches a presynaptic terminal, it causes vesicles near the presynaptic membrane to fuse with the membrane and discharge their contents into the synaptic cleft. The key event in this process is an influx of calcium ions (Ca^{2+}), rather than K$^+$ or Na$^+$, into the axon terminal. These cations enter through voltage-gated Ca^{2+} channels that open in response to the arrival of an action potential. The higher the frequency of action potentials arriving at the terminal, the greater the influx of Ca^{2+}, and the greater the number of vesicles that dump their contents into the synapse. Most synaptic delay is caused by the time needed for Ca^{2+} to enter the terminal. Diffusion of the transmitter across the cleft, and the interaction of transmitter molecules with their receptors, also introduces some delay.

Synaptic vesicles are about 50 nanometers (nm) in diameter, and are quite complex structures; one important component is a protein called *synaptotagmin* that binds Ca^{2+}. Because all the synaptic vesicles in an axon terminal contain about the same number of molecules of transmitter—estimated to be tens of thousands—they all produce about the same change in postsynaptic potential when they rupture and release their contents. Normally an action potential causes the release of several hundred vesicles at a time. But if the extracellular concentration of calcium is experimentally lowered, only a few vesicles are released from the terminal per action potential, and the magnitude of change in postsynaptic potential associated with the contents of one vesicle can then be calculated.

The presynaptic terminal normally produces and stores enough transmitter to ensure that it is ready for activity. Intense activity of the neuron reduces the number of available vesicles, but soon more vesicles are produced to replace those that were discharged. Neurons differ in their ability to keep pace with a rapid rate of incoming action potentials. Furthermore, the rate of production of the transmitter chemical is governed by enzymes that are manufactured in the neuronal cell body and transported actively down the axons to the terminals. A neuron's maximal rate for producing and transporting these vital substances partly determines how long the neuron can sustain high levels of synaptic activity before becoming fatigued and less responsive to stimulation.

Receptor molecules recognize transmitters

The action of a key in a lock is a good analogy for the action of a transmitter on a receptor protein. Just as a particular key can open different doors, a molecule of the correct shape, called a **ligand** (see Chapter 4), can fit into a receptor protein and activate or block it. Neurotransmitters and hormones made inside the body are examples of **endogenous ligands**; drugs and toxins from outside the body are **exogenous ligands**. So, for example, at synapses where **acetylcholine (ACh)** is the transmitter, it fits into *ligand-binding sites* in **receptor molecules** located in the postsynaptic membrane (**Figure 3.12**).

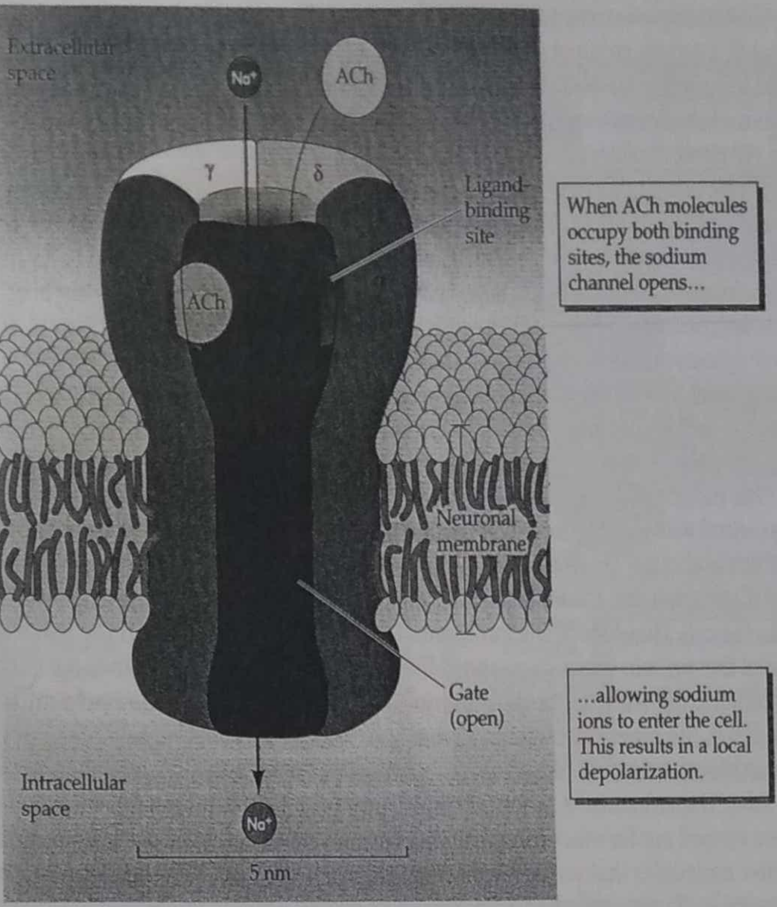
ligand A substance that binds to receptor molecules, such as those at the surface of the cell.

endogenous ligand Any substance, produced within the body, that selectively binds to the type of receptor that is under study.

exogenous ligand Any substance, originating from outside the body, that selectively binds to the type of receptor that is under study.

acetylcholine (ACh) An amine transmitter that stimulates muscle contraction, but is also found throughout the brain.

receptor molecule Also called *receptor*. A protein that captures and reacts to molecules of the transmitter or hormone.



When ACh molecules occupy both binding sites, the sodium channel opens...

...allowing sodium ions to enter the cell. This results in a local depolarization.

3.12 A Nicotinic Acetylcholine Receptor Each nicotinic ACh receptor consists of five subunits. The two ligand-binding sites normally bind ACh molecules, but they also bind nicotine and other nicotinic drugs. The ACh molecule and Na^+ ions are enlarged here for diagrammatic purposes.

The nature of the postsynaptic receptors at a given synapse determines the action of the transmitter (see Chapter 4). For example, ACh can function as either an inhibitory or an excitatory neurotransmitter, at different synapses. At excitatory synapses, binding of ACh opens channels for Na^+ and K^+ ions. At inhibitory synapses, ACh opens channels that allow chloride ions (Cl^-) to enter, thereby hyperpolarizing the membrane (i.e., making it more negative).

The lock-and-key analogy is strengthened by the observation that various chemicals can fit onto receptor proteins and block the entrance of the key. Some of the preparations used in this research resemble the ingredients of a witches' brew. As an example, consider a couple of potent poisons that block ACh receptors: curare and bungarotoxin. **Curare** is an arrowhead poison used by native South Americans. Extracted from a plant, it greatly increases the efficiency of hunting: if the hunter hits any part of the prey, the arrow's poison soon paralyzes the animal. **Bungarotoxin**, another blocker of acetylcholine receptors, is found in the venom of the banded krait (*Bungarus multicinctus*), a snake native to Taiwan. This toxin has proved very useful in research because a radioactive label can be attached to molecules of bungarotoxin without causing any change in their function. The labeled bungarotoxin can then be used to study the number, distribution, and functioning of acetylcholine receptor molecules.

Another poison, muscarine, mimics the action of ACh at some synapses. This poison is extracted from the mushroom *Amanita muscaria*. Molecules such as muscarine and nicotine that act like a transmitter at a receptor are called **agonists** (from the Greek *agon*, "contest" or "struggle") of that transmitter. Conversely, molecules that interfere with or prevent the action of a transmitter, in such a manner as curare or bungarotoxin block the action of ACh, are called **antagonists**.

curare An alkaloid neurotoxin that causes paralysis by blocking acetylcholine receptors in muscle.

bungarotoxin A neurotoxin, isolated from the venom of the banded krait, that selectively blocks acetylcholine receptors.

agonist A molecule, usually a drug, that binds a receptor molecule and initiates a response like that of another molecule, usually a neurotransmitter.

antagonist A molecule, usually a drug, that interferes with or prevents the action of a transmitter.

Just as there are master keys that fit many different locks, there are submaster keys that fit a certain group of locks, and keys that fit only a single lock. Similarly, each chemical transmitter binds to several different receptor molecules. ACh acts on at least four kinds of **cholinergic** receptors; nicotinic and muscarinic are the two main kinds.

Nicotinic cholinergic receptors are found at synapses on skeletal muscles and in autonomic ganglia; it is the blockade of these receptors that is responsible for the paralysis caused by curare and bungarotoxin. Muscarinic cholinergic receptors are found on organs innervated by the parasympathetic division of the autonomic system (e.g., the heart muscle, the intestines, and the salivary gland). Most ACh receptors in the brain, too, are muscarinic. Most nicotinic sites are excitatory, but there are also inhibitory nicotinic synapses, and there are both excitatory and inhibitory muscarinic synapses, making at least four kinds of acetylcholine receptors. The existence of many types of receptors for each transmitter agent has evolved to provide specificity of transmitter action in the nervous system.

The nicotinic ACh receptor resembles a lopsided dumbbell with a tube running down its central axis (see Figure 3.12). The handle of the dumbbell spans the cell membrane (which is about 6 nm thick); the larger sphere extends about 5 nm above the surface of the membrane into the extracellular space, and the smaller sphere extends about 2 nm into the cell. The sides of the ion channel (the tube that runs through the handle) consist of five protein subunits arranged like staves in a barrel. Two subunits are alike and, in conjunction with neighboring subunits, provide two recognition sites for ACh (Karlin, 2002); the other three subunits are all different. Both ACh-binding sites must be occupied for the channel to open.

After the structure of the nicotinic ACh receptor was determined, similar analyses were carried out for other receptors, including receptors for some of the synaptic transmitter molecules that we will be considering later, such as GABA (gamma–aminobutyric acid), glycine, and glutamate. Several of these receptors resemble each other, suggesting that they all belong to the same family and have a common evolutionary origin.

The coordination of different transmitter systems of the brain is incredibly complex. Each subtype of neurotransmitter receptor has a unique pattern of distribution within the brain. Different receptor systems become active at different times in fetal life. The number of any given type of receptor remains plastic in adulthood: not only are there seasonal variations, but many kinds of receptors show a regular daily variation of 50% or more in number, affecting the sensitivity of cells to that variety of transmitter. Similarly, the numbers of some receptors have been found to vary with the use of drugs (see Chapter 4). In general, an increase in receptor numbers is referred to as **up-regulation**, and a process that decreases receptor density is called **down-regulation** of that receptor type.

Transmitters bind to receptors, gating ion channels

The recognition of transmitter molecules by receptor molecules controls the opening of ion channels in two different ways. **Ionotropic receptors** (**Figure 3.13*a***) directly control an ion channel. When bound by the transmitter, the ion channel opens and ions flow across the membrane. (Ionotropic receptors are also known as chemically gated ion channels, or **ligand-gated ion channels**.) **Metabotropic receptors** (**Figure 3.13*b***) recognize the synaptic transmitter, but they do not directly control ion channels. Instead they activate molecules known as **G proteins**.

G protein is a convenient designation for proteins that bind the compounds guanosine diphosphate (GDP), guanosine triphosphate (GTP), and other guanine nucleotides. Sometimes the G protein itself acts to open ion channels, but in other cases the G protein activates another, internal chemical signal to affect ion channels. If we think of the transmitter-activated G protein as the first messenger inside the postsynaptic cell, then the next chemical activated within the cell is a **second messenger**. Several different second messengers—such as cyclic adenosine monophosphate (cyclic AMP), diacylglycerol, or arachidonic acid—amplify the effect of the first messenger and can initiate processes that lead to changes in electrical potential at the membrane. An important

cholinergic Referring to cells that use acetylcholine as their synaptic transmitter.

up-regulation A compensatory increase in receptor availability at the synapses of a neuron.

down-regulation A compensatory reduction in receptor availability at the synapses of a neuron.

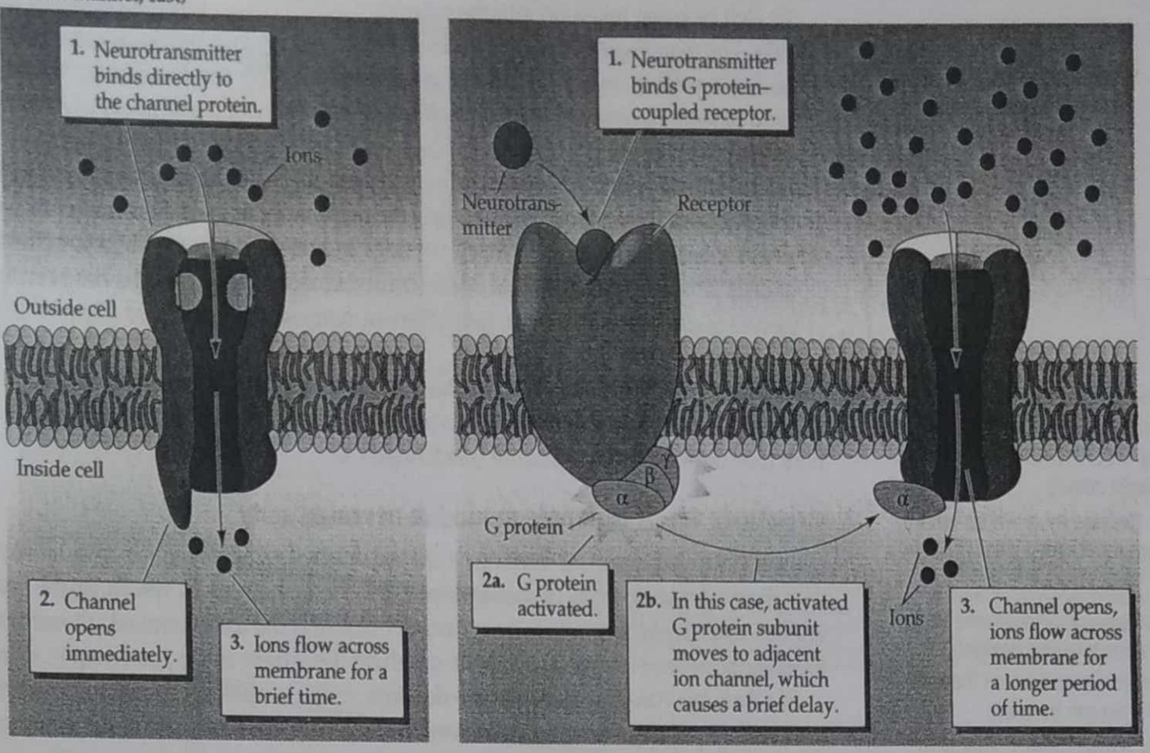
ionotropic receptor A receptor protein that includes an ion channel that is opened when the receptor is bound by an appropriate ligand.

ligand-gated ion channel An ion channel that opens or closes in response to the presence of a particular chemical.

metabotropic receptor A type of transmitter receptor that does not contain an ion channel but may, when activated, use a G protein system to alter the functioning of the postsynaptic cell.

G proteins A class of proteins that reside next to the intracellular portion of a receptor and that are activated when the receptor binds an appropriate ligand on the extracellular surface.

second messenger A slow-acting substance in the postsynaptic cell that amplifies the effects of synaptic activity and signals synaptic activity within the postsynaptic cell.



(*a*) **Ionotropic receptor (ligand-gated ion channel; fast)**

(*b*) **Metabotropic receptor (G protein–coupled receptor; slow)**

1. Neurotransmitter binds directly to the channel protein.
Ions
Outside cell
Inside cell
2. Channel opens immediately.
3. Ions flow across membrane for a brief time.
1. Neurotransmitter binds G protein–coupled receptor.
Neurotransmitter
Receptor
β
γ
α
G protein
2a. G protein activated.
2b. In this case, activated G protein subunit moves to adjacent ion channel, which causes a brief delay.
α
Ions
3. Channel opens, ions flow across membrane for a longer period of time.

3.13 Two Types of Chemical Synapses

feature of second-messenger systems is their ability to amplify and prolong the synaptic signals that a neuron receives.

About 80% of the known neurotransmitters and hormones activate cellular signal mechanisms through receptors coupled to G proteins, so this coupling device is very important (Birnbaumer et al., 1990). The G protein is located on the inner side of the neural membrane. When a transmitter molecule binds to a receptor that is coupled to a G protein, parts of the G protein complex separate from each other. One part, called the *alpha subunit*, migrates away within the cell and modulates the activity of its target molecules. Depending on the type of cell and receptor, the target may be a second-messenger system, an enzyme that works on an ion channel, or an ion pump. Many combinations of different receptors with different G proteins have already been identified, and more are being discovered at a rapid pace (Fredriksson et al., 2003; Gudermann et al., 1997; Wettschurek and Offermanns, 2005).

The action of synaptic transmitters is stopped rapidly

When a chemical transmitter such as ACh is released into the synaptic cleft, its postsynaptic action is not only prompt, but usually very brief as well. This brevity ensures that the message is repeated faithfully. Accurate timing of synaptic transmission is necessary in many neural systems—for example, to drive the rapid cycles of muscle contraction and relaxation essential to many coordinated behaviors.

The prompt cessation of transmitter effects is achieved in one of two ways:

1. *Degradation*. Transmitter can be rapidly broken down and thus inactivated by a special enzyme—a process known as **degradation** (step 6a in Figure 3.11). For example, the enzyme that inactivates ACh is acetylcholinesterase (AChE). Acetylcholinesterase breaks down ACh very rapidly into choline and acetic acid, and these products are recycled (at least in part) to make more ACh in the axon terminal. AChE is found especially at synapses, but also elsewhere in the nervous system. Thus, if any ACh escapes from a synapse where it is released, it is unlikely to reach other synapses intact, where it could start false messages.

degradation The process by which neurotransmitter molecules are broken down into inactive metabolites.

reuptake The process by which released synaptic transmitter molecules are taken up and reused by the presynaptic neuron, thus stopping synaptic activity.

pinocytosis The process by which synaptic neurotransmitter is repackaged into synaptic vesicles.

transporters Specialized receptors in the presynaptic membrane that recognize transmitter molecules and return them to the presynaptic neuron for reuse.

axo-dendritic Referring to a synapse in which a presynaptic axon terminal synapses onto a dendrite of the postsynaptic neuron, either via a dendritic spine or directly onto the dendrite itself.

axo-axonic Referring to a synapse in which a presynaptic axon terminal synapses onto another axon's terminal.

dendro-dendritic Referring to a type of synapse in which a synaptic connection forms between the dendrites of two neurons.

retrograde synapse A synapse in which a signal (usually a gas neurotransmitter) flows from the postsynaptic neuron to the presynaptic neuron, thus counter to the usual direction of synaptic communication.

ectopic transmission Cell–cell communication based on release of neurotransmitter in regions outside traditional synapses.

varicosity The axonal swelling from which neurotransmitter diffuses in a nondirected synapse.

nondirected synapse A type of synapse in which the presynaptic and postsynaptic cells are not in close apposition; instead, neurotransmitter is released by axonal varicosities and diffuses away to affect wide regions of tissue.

neural chain A simple kind of neural circuit in which neurons are attached linearly, end to end.

knee jerk reflex A variant of the stretch reflex in which stretching of the tendon beneath the knee leads to an upward kick of the leg.

2. *Reuptake.* Alternatively, transmitter molecules may be rapidly cleared from the synaptic cleft by being taken up into the presynaptic terminal—a process known as **reuptake**. The repackaging of released transmitter molecules into vesicles is called **pinocytosis** (step 6b in Figure 3.11), and allows for recycling the transmitter chemical. Norepinephrine, dopamine, and serotonin are examples of transmitters whose activity is terminated mainly by reuptake. In these cases, special receptors for the transmitter, called **transporters**, are located on the presynaptic axon terminal and bring the transmitter back inside. Once taken up into the presynaptic terminal, transmitter molecules may be repackaged into synaptic vesicles and released when additional action potentials arrive at the terminal. Malfunction of reuptake mechanisms has been suspected to cause some kinds of mental illness, such as depression (see Chapter 16).

In many cases, neurons are also influenced by neuromodulators, substances that by themselves do not produce significant neural effects but that bind to receptors to change how they respond to a transmitter (see Chapter 4).

Nonclassic forms of synapses modulate neural activity

For simplicity, we have been focusing on the classic, directed **axo-dendritic** synapse. However, many nonclassic forms of chemical synapses exist in the nervous system. As the name implies, **axo-axonic** synapses form on axons, often near the axon terminal, allowing the presynaptic neuron to strongly facilitate or inhibit the activity of the postsynaptic axon.

Similarly, neurons may form **dendro-dendritic** contacts, allowing coordination of their activities. At a **retrograde synapse**, transmission starts with classic axo-dendritic synaptic activity, but the postsynaptic cell subsequently releases a gas neurotransmitter, such as carbon monoxide or nitric oxide (see Chapter 4), which signals the presynaptic cell to release more transmitter.

Evidence is also mounting that **ectopic transmission** occurs between many neurons; in this mode of transmission, the location of transmitter release and the sites at which the transmitter acts are both well outside the conventional boundaries of nearby synapses (Coggan et al., 2005). And throughout the brain are found axons with regular swellings, called **varicosities**, along their length; like a drip-irrigation system, these **nondirected synapses** steadily release neurotransmitter to broadly affect surrounding areas.

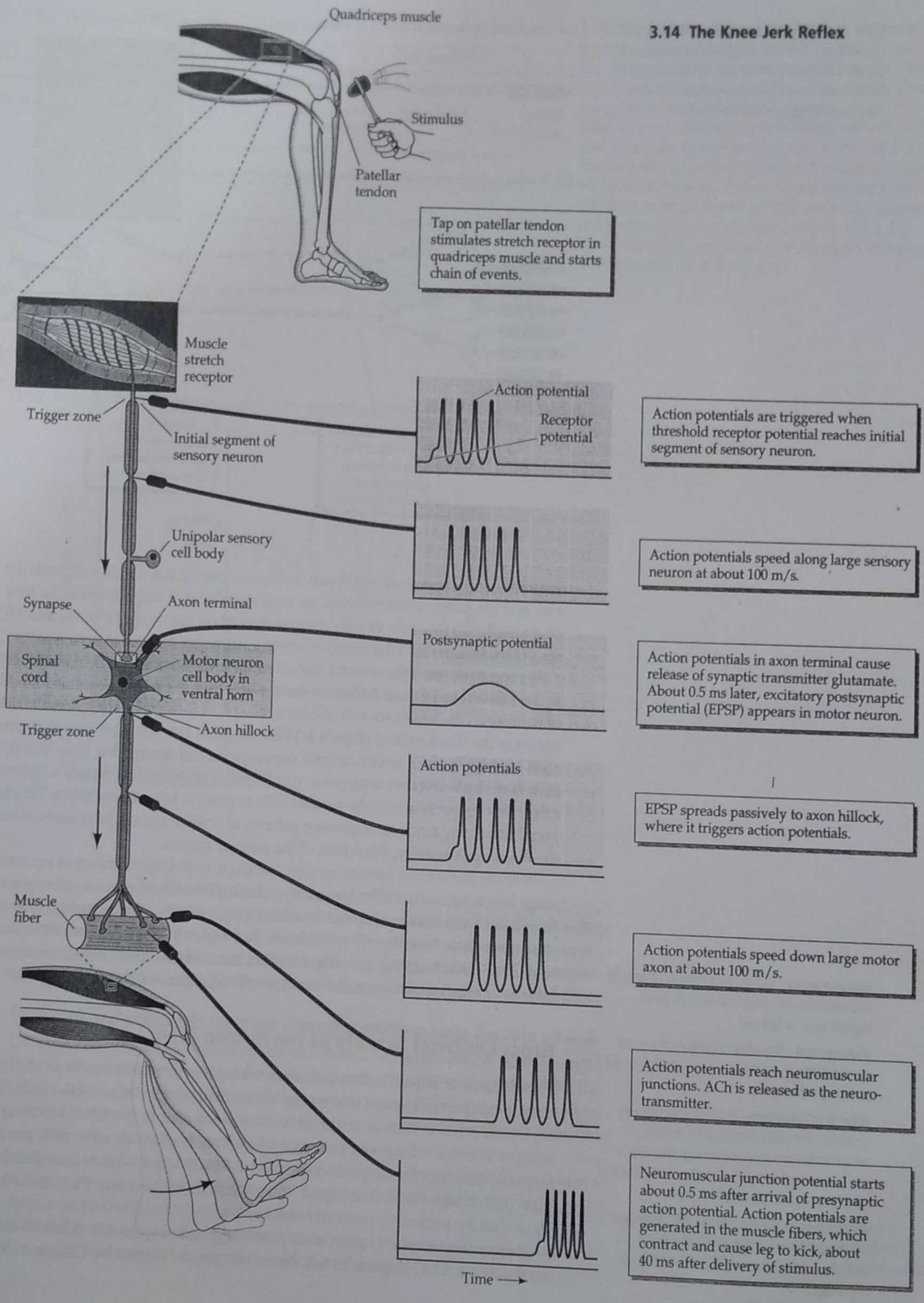
Neurons and Synapses Combine to Make Circuits

Use of the term *circuit* for an assemblage of neurons and their synaptic interconnections is an analogy to electrical or electronic circuits, in which an arrangement of components (e.g., resistors, capacitors, transistors, and their connecting wires) accomplishes a particular function. Electrical or electronic circuits can represent signals in either analog or digital ways—that is, in terms of continuously varying values or in terms of integers. Neurons similarly feature two kinds of processes: analog-like signals that vary in strength (such as graded potentials at synapses) and digital-like all-or-nothing signals (such as action potentials) that vary in frequency. The nervous system comprises many different types of neural circuits that use both types of processes to accomplish basic functions in cognition, emotion, and action—all the categories of behavior and experience.

The simplest neural circuit that is routinely encountered in the nervous system is the **neural chain**, a straightforward linking of a series of neurons. (A look at some other simple neural circuits is presented on the website in **A Step Further: Circuits of Neurons Process Information**.) From the seventeenth century until well into the twentieth century, most attempts to understand behavior in neural terms were based on chains of neurons, which do indeed account for some behaviors. For example, the basic circuit for the stretch reflex, such as the **knee jerk reflex**, consists of a sensory neuron, a motor neuron, and a single synapse where the sensory neuron communicates with the motor neuron. Hundreds or thousands of such circuits work in parallel to enable the stretch reflex.

Figure 3.14 shows the sequence and timing of events in the knee jerk reflex. Note that this reflex is extremely rapid: only about 40 ms elapse between the stimulus and

3.14 The Knee Jerk Reflex


Quadriceps muscle
Stimulus
Patellar tendon
Muscle stretch receptor
Trigger zone
Initial segment of sensory neuron
Action potential
Receptor potential
Unipolar sensory cell body
Synapse
Axon terminal
Spinal cord
Motor neuron cell body in ventral horn
Postsynaptic potential
Trigger zone
Axon hillock
Action potentials
Muscle fiber
Time ⟶

Tap on patellar tendon stimulates stretch receptor in quadriceps muscle and starts chain of events.

Action potentials are triggered when threshold receptor potential reaches initial segment of sensory neuron.

Action potentials speed along large sensory neuron at about 100 m/s.

Action potentials in axon terminal cause release of synaptic transmitter glutamate. About 0.5 ms later, excitatory postsynaptic potential (EPSP) appears in motor neuron.

EPSP spreads passively to axon hillock, where it triggers action potentials.

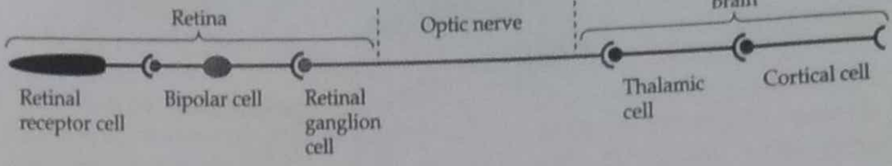
Action potentials speed down large motor axon at about 100 m/s.

Action potentials reach neuromuscular junctions. ACh is released as the neurotransmitter.

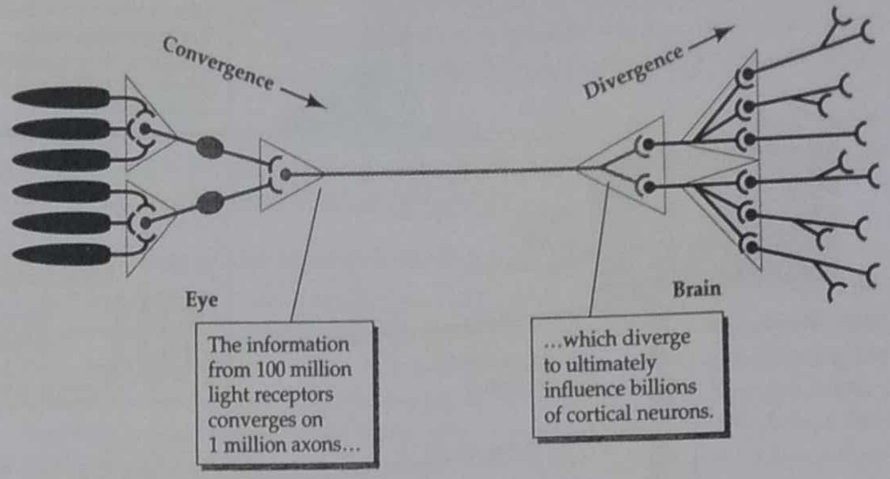
Neuromuscular junction potential starts about 0.5 ms after arrival of presynaptic action potential. Action potentials are generated in the muscle fibers, which contract and cause leg to kick, about 40 ms after delivery of stimulus.

3.15 Two Representations of Neural Circuitry (*a*) This simple representation shows the input part of the visual system. (*b*) This more complex representation illustrates convergence and divergence.

(*a*) The visual system represented as a neural chain



(*b*) A more realistic representation, showing convergence and divergence



The information from 100 million light receptors converges on 1 million axons...

...which diverge to ultimately influence billions of cortical neurons.

the initiation of the response. Several factors account for this rapidity: (1) both the sensory and the motor axons involved are myelinated and of large diameter, so they conduct rapidly; (2) the sensory cells synapse directly on the motor neurons; and (3) both the central synapse and the neuromuscular junction are fast, ionotropic synapses.

For some purposes the afferent (input) parts of the visual system can be represented as a neural chain (**Figure 3.15*a***) (in reality, however, the retina contains many kinds of neural circuits, which we will discuss in Chapter 10). A more accurate schematic diagram of the visual system (**Figure 3.15*b***) brings out two other features that are common to many kinds of neural circuits: **convergence** and **divergence**. Note that in these circuits multiple units are arranged in parallel; such systems often feature additional circuitry that connects across the parallel cells to provide **lateral interaction**. This type of initial processing tends to emphasize patterns of activity across a large array, which has the effect of sharpening the tuning of the sensory system.

In many parts of the nervous system, the axons from large numbers of neurons converge on certain cells. In the human eye, about 100 million receptor cells concentrate their information down on about 1 million ganglion cells; these ganglion cells convey the information from the eye to the brain (see Figure 3.15*b*). Higher in the visual system there is much divergence: the 1 million axons of the optic nerve communicate to billions of neurons in several different specialized regions of the cerebral cortex.

convergence The phenomenon of neural connections in which many cells send signals to a single cell.

divergence The phenomenon of neural connections in which one cell sends signals to many other cells.

lateral interaction Especially in sensory systems, the phenomenon by which reciprocal connections among neurons at the same level in the hierarchy more sharply tune the responses of the system.

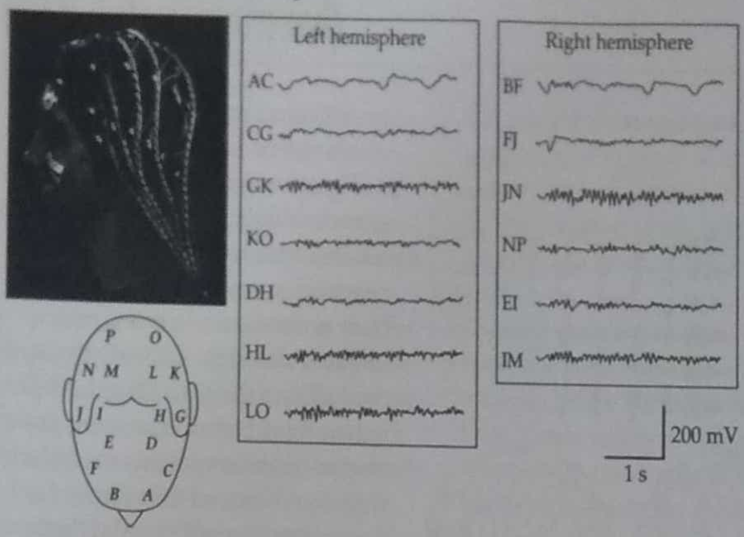
Gross Electrical Activity of the Human Brain

The electrical activity of millions of cells working together combines to produce electrical potentials large enough that we can detect them at the surface of the skull. Recordings of electrical activity in the brain that are made with large electrodes either on the scalp or within the brain can provide useful glimpses of the simultaneous workings of large populations of neurons. Investigators divide these gross brain potentials into two principal classes: those that appear spontaneously without specific stimulation, and those that are evoked by particular stimuli.

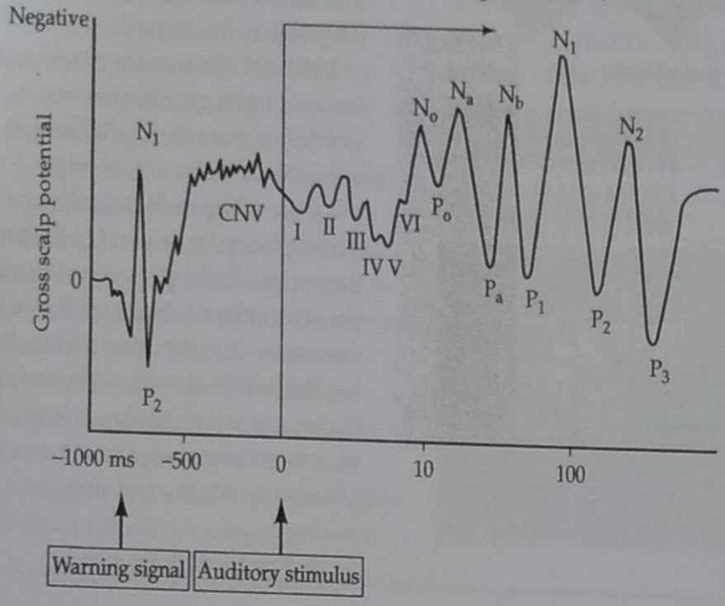
A recording of spontaneous brain potentials, or *brain waves*, is called an **electroencephalogram (EEG)** (**Figure 3.16*a***). As we will see in Chapter 14, EEG recordings of a

electroencephalogram (EEG) A recording of gross electrical activity of the brain recorded from large electrodes placed on the scalp.

(a) Multichannel EEG recording



(b) Event-related potentials (average of many stimulus presentations)



3.16 Gross Potentials of the Human Nervous System (a) (*Top left*) Electrode array for EEG recording. (*Bottom left*) Each electrode can be assigned a letter on a map of the scalp. (*Right*) Typical EEG records showing potential measured between various points on the scalp. (*b*) Event-related potentials (average of many stimulus presentations). Following stimulus presentation, a fixed sequence of processing-related potentials is generated. Early components (labeled I–VI) are associated with brainstem activity, followed by large-amplitude negative- and positive-voltage events (labeled N_0–N_2 and P_0–P_3). The longer-latency components are associated with cognitive processing of task demands.

sleeping person allow investigators to distinguish different kinds and stages of sleep. Brain potentials also provide significant diagnostic data—for example, in distinguishing forms of seizure disorders (**Box 3.3**). In addition, they provide prognostic data, such as predictions of the functional effects of brain injury. In many jurisdictions, EEGs are used to determine death according to the legal definition.

Event-related potentials measure changes resulting from discrete stimuli

Gross potential changes evoked by discrete stimuli—usually sensory stimuli, such as light flashes or clicks—are called **event-related potentials (ERPs)** (**Figure 3.16*b***). Typically in experiments that exploit this phenomenon, many ERPs are averaged to obtain a reliable estimate of stimulus-elicited brain activity. Sensory-evoked potentials have very distinctive characteristics of wave shape and latency that reflect the type of stimulus, the state of the subject, and the site of recording. Subtler psychological processes, such as expectancy (anticipation that something is about to happen), also appear to influence some characteristics of evoked potentials.

Computer techniques enable researchers to record brain potentials using electrodes that are located a significant distance from the sites at which the potentials are gener-

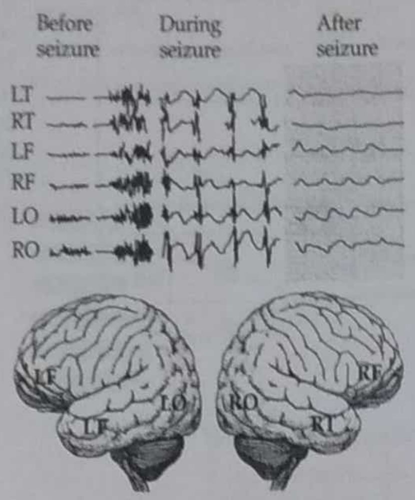
event-related potential (ERP) A large change in electrical potential in the brain that is elicited by a discrete sensory or motor event.

BOX 3.3 Seizure Disorders

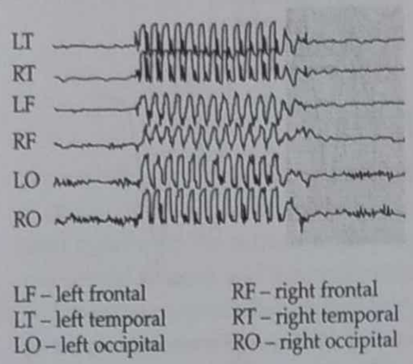
Epilepsy (from the Greek *epilepsia*, a form of the verb meaning "to seize") has provoked wonder and worry since the dawn of civilization. Through the ages the seizures that accompany this disease have spawned much speculation about the cause—from demons to gods. About 30 million people, worldwide, suffer from epilepsy.

Seizures are an unfortunate manifestation of the electrical character of the nervous system. Because of the extensive connections among its nerve cells, the brain can generate massive waves of intense nerve cell activity that seem to involve almost the entire brain. In the normal, active brain, electrical activity tends to be desynchronized; that is, different brain regions carry on their functions more or less independently. In contrast, a **seizure** features widespread synchronization of electrical activity: broad swaths of the brain start firing in simultaneous waves of excitation, which are evident in the EEGs as an abnormal "spike-and-wave" pattern of brain activity. Many abnormalities of the brain, such as trauma, injury, or metabolic problems, can predispose brain tissue to produce synchronized *epileptiform* activity, which can easily spread.

(A) Grand mal seizure



(B) Petit mal seizure



There are several major categories of seizure disorders. Generalized seizures are characterized by loss of consciousness and symmetrical involvement of body musculature. In **grand mal seizures**, abnormal EEG activity is evident all over the brain (Figure A). The person loses consciousness and makes characteristic movements: an enduring *tonic* contraction of the muscles for 1 or 2 minutes, followed by jerky, rhythmic *clonic* contractions and relaxations. Minutes or hours of confusion and sleep follow the seizure.

Petit mal seizures are a more subtle variant of generalized seizures, in which the characteristic spike-and-wave EEG activity is evident for 5 to 15 s at a time (Figure B), sometimes occurring many times per day. During these periods the person is unaware of the environment, and later the person cannot recall events that occurred during the petit mal episode. Behaviorally, the person does not show unusual muscle activity, except for a cessation of ongoing activity and sustained staring.

ated. An example that has attracted considerable research and clinical attention is *auditory-evoked brainstem potentials* (see Figure 3.16*b*). The neural generators of these waves are located far from the site of recording—in the auditory nerve and successive levels of the auditory pathway in the brainstem. These ERPs provide a way to assess the integrity and functioning of the brainstem and especially its auditory pathways. For example, decreases in the amplitude of certain waves or increases in their latency have been valuable in detecting hearing impairments in very young children and noncommunicative persons. Infants with impaired hearing produce reduced auditory ERPs or no ERP at all in response to sounds. Another use of ERPs is in the assessment of brainstem injury or damage.

The long-latency components of scalp-recorded ERPs are thought to reflect the operation of information-processing mechanisms of the brain, such as attention, decision making, and other complex cognitive processes. In contrast, short-latency responses are determined more by exogenous factors, such as the physical characteristics of the stimulus. For example, dimensions like stimulus intensity have a bigger effect on early components of ERPs than on longer-latency components.

Although it is usually difficult to localize which brain region has produced a given component of the ERP, such changes are detected quickly, within a fraction of a second. In contrast, computer-coordinated imaging of brain activity, such as functional MRI

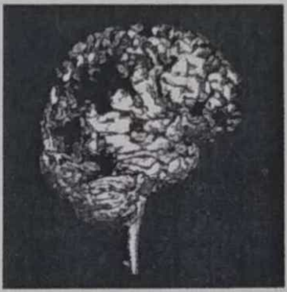
BOX 3.3 (continued)

Complex partial seizures do not involve the entire brain and thus can produce a wide variety of symptoms, often preceded by an unusual sensation or **aura**. In one example, a woman felt an unusual sensation in the abdomen, a sense of foreboding, and tingling in both hands before the seizure spread. At the height of it, she was unresponsive and rocked her body back and forth while speaking nonsensically, twisting her left arm, and looking toward the right. Figure C is a three-dimensional reconstruction showing where the seizures occurred in her brain. In some individuals, complex partial seizures may be provoked by environmental stimuli and may produce strikingly abnormal behavior.

Seizures affect nonhuman animals, too, and such cases are studied as a model of human epilepsy. In **kindling** (McNamara, 1984), animals receive repeated electrical stimulation that is too weak to cause a seizure on its own. Eventually, although the individual stimuli are small, the accumulated effect is that spontaneous seizures appear. In other words, the kindling stimulations somehow change the tissue and make it more epilepsy-prone. Interestingly, after years of epilepsy, some human patients develop multiple foci for the initiation of seizures, perhaps because of a kindling process (Morrell, 1991).

Many seizure disorders can be effectively controlled with the aid of anti-epileptic drugs. Although these drugs have a wide variety of different targets, they have in common a tendency to selectively modulate the excitability of neurons, either by counteracting problems with ionic balance (see Box 3.1) or by promoting inhibitory processes (Rogawski and Löscher, 2004). (Figure C courtesy of Hal Blumenfeld, Rik Stokking, Susan Spencer, and George Zubal, Yale School of Medicine.)

(C) Complex partial seizure



epilepsy A brain disorder marked by major sudden changes in the electrophysiological state of the brain that are referred to as seizures.

seizure An epileptic episode.

grand mal seizure A type of generalized epileptic seizure in which nerve cells fire in high-frequency bursts.

petit mal seizure Also called an *absence attack*. A seizure that is characterized by a spike-and-wave EEG and often involves a loss of awareness and inability to recall events surrounding the seizure.

complex partial seizure In epilepsy, a type of seizure that doesn't involve the entire brain, and therefore can cause a wide variety of symptoms.

aura In epilepsy, the unusual sensations or premonition that may precede the beginning of a seizure.

kindling A method of experimentally inducing an epileptic seizure by repeatedly stimulating a brain region.

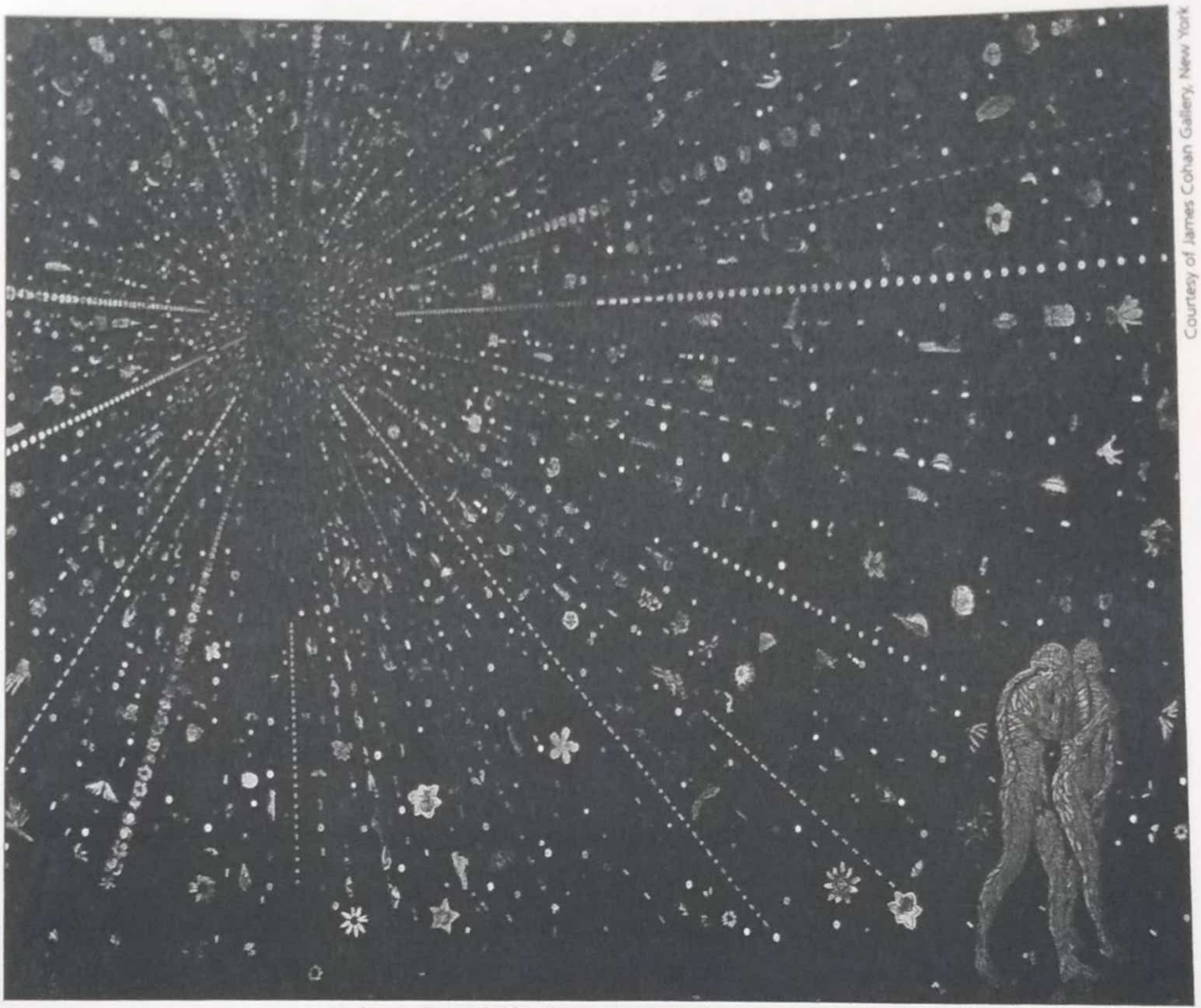
(fMRI) (see Chapter 2), indicates clearly which brain region is active, but because such imaging techniques must average activity over seconds or minutes, they are slower than ERPs. Perhaps the greatest promise for future research is a melding of the two techniques—combining techniques that measure rapid changes in electrical activity, such as ERPs and magnetoencephalography (see Chapter 2), with slower but higher-resolution techniques such as fMRI or PET scans to identify probable sites of origin of the evoked activity (e.g., Liebenthal et al., 2003). These techniques have given us a better glimpse of brain functioning than Otto Loewi ever imagined.

Summary

1. Nerve cells are specialized for receiving, processing, and transmitting signals.
2. Neurons exhibit a small electrical potential across the cell membrane; neural signals are changes in this potential.
3. The different concentrations of ions inside and outside the neuron—especially potassium ions (K^+), to which the resting membrane is selectively permeable—account for the resting potential. At equilibrium, the electrostatic pressure pulling K^+ ions into the neuron is balanced by the concentration gradient pushing them out; at this point, the membrane potential is about –60 mV, the resting potential.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

CHAPTER 4



Courtesy of James Cohan Gallery, New York

Fred Tomaselli, *Untitled (Expulsion)*, 2000, photocollage, leaves, pills, insects, acrylic, resin on wood panel, 84 × 120 in.

CONTENTS

Many Chemical Neurotransmitters Have Been Identified 89

Neurotransmitter Systems Form a Complex Array in the Brain 91

Research on Drugs Ranges from Molecular Processes to Effects on Behavior 95

Drugs Affect Each Stage of Neural Conduction and Synaptic Transmission 101

Drugs That Affect the Brain Can Be Divided into Functional Classes 103

Drug Abuse Is Pervasive 111

The Chemical Bases of Behavior: Neurotransmitters and Neuropharmacology

The Birth of a Pharmaceutical Problem Child

In the 1930s and 1940s, Swiss pharmacologist Albert Hofmann was working for Sandoz Pharmaceuticals and studying compounds derived from ergot, a fungus that grows on grain, in the hope of synthesizing new and useful drugs from it. One day in April of 1943, Dr. Hofmann began to feel unwell at work and, believing he was coming down with a cold, he left for home. However, he soon began experiencing bizarre visual phenomena: "an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors" (Hofmann, 1981). When he closed his eyes, the luridly colored, oddly shifting forms seemed to surge toward him. The state lasted about 2 hours. Suspecting that he had accidentally ingested a small amount of an experimental compound, Hofmann began to research its properties.

Although one could debate the wisdom of testing unknown drugs on oneself, Hofmann was breaking no laws in force at the time. When he self-administered even a seemingly tiny dose, he nonetheless experienced incapacitating changes in brain function and astonishing, sometimes frightening, visual apparitions. In addition to the visual phenomena, he reported sometimes feeling that his sense of self was "loosened." Careful analyses later revealed the new drug to be amazingly potent: a few millionths of a gram was enough to induce substantial effects. What was this substance? By what mechanisms did it affect the brain?

As far back as we can trace human history, people have tasted, sipped, chewed, or swallowed all kinds of substances—animal, vegetable, and mineral. From these experiences, people have learned to consume some substances and shun others. Social customs and dietary codes evolved to protect people from consuming harmful substances. This long history of seeking, testing, and using different substances came not only from the need for nourishment but also from the desire to relieve pain, control anxiety, and pursue pleasure. But we are not alone in this activity; "almost every species of animal has engaged in the natural pursuit of intoxicants" (R. K. Siegel, 1989, p. viii).

The functioning brain is an electrochemical system, so it's no surprise that most drugs that affect the nervous system do so by altering brain chemistry and synaptic transmission. We begin our tour of **neurochemistry** and **neuropharmacology** by delving more deeply into the neurotransmitter systems that we introduced in Chapter 3. Then we review some of the major classes of drugs that affect the nervous system and behavior, and finally we turn to mechanisms of drug abuse and dependency.

Many Chemical Neurotransmitters Have Been Identified

We learned in Chapter 3 that neurons release a chemical known as a *neurotransmitter* (or simply *transmitter*) to communicate with target cells, usually other neurons. Identifying neurotransmitters and understanding how they act are continuing quests.

What are the criteria for deciding that a substance acts as a neurotransmitter? To classify a substance as a classic neurotransmitter, we must show that

- The substance exists in the presynaptic axon terminals.
- The presynaptic cell contains appropriate enzymes for synthesizing the substance.
- The substance is released in significant quantities when action potentials reach the terminals.

neurochemistry The branch of neuroscience concerned with the fundamental chemical composition and processes of the nervous system.

neuropharmacology Also called *psychopharmacology*. The scientific field concerned with the discovery and study of compounds that selectively affect the functioning of the nervous system.

TABLE 4.1 Some Synaptic Transmitters and Families of Transmitters

Family and subfamily	Transmitter(s)
AMINES	
Quaternary amines	Acetylcholine (ACh)
Monoamines	*Catecholamines*: Norepinephrine (NE), epinephrine (adrenaline), dopamine (DA) *Indoleamines*: Serotonin (5-hydroxytryptamine; 5-HT), melatonin
AMINO ACIDS	Gamma-aminobutyric acid (GABA), glutamate, glycine, histamine
NEUROPEPTIDES	
Opioid peptides	*Enkephalins*: Met-enkephalin, leu-enkephalin *Endorphins*: β-endorphin *Dynorphins*: Dynorphin A
PEPTIDES	Oxytocin, substance P, cholecystokinin (CCK),vasopressin, neuropeptide Y (NPY), hypothalamic releasing hormones
GASES	Nitric oxide, carbon monoxide

- Specific receptors that recognize the released substance exist on the postsynaptic membrane.
- Experimental application of the substance produces changes in postsynaptic potentials.
- Blocking release of the substance prevents presynaptic nerve impulses from altering the activity of the postsynaptic cell.

Table 4.1 summarizes the major categories of the many neurotransmitters that we already know about. Substances that satisfy the criteria for transmitters include various **amine neurotransmitters**, such as acetylcholine, dopamine, and serotonin; **amino acid neurotransmitters** like GABA and glutamate; and a wide variety of **peptide neurotransmitters**, made up of short chains of amino acids. As the search goes on, the number of probable synaptic transmitters continues to grow, and occasionally yields surprises like the **gas neurotransmitters**, soluble gases that diffuse between neurons to alter ongoing processes.

Even if a substance is known to be a transmitter in one location, proving that it acts as a transmitter at another location where it is found may be difficult. For example, acetylcholine was long accepted as a transmitter agent in the peripheral nervous system (remember Otto Loewi's discoveries recounted in Chapter 3), but it was harder to prove that acetylcholine serves as a transmitter in the central nervous system as well. Now it is recognized that acetylcholine is widely distributed in the brain, and its possible relationship to the cognitive deficits seen in Alzheimer's disease is the subject of much current work. Considering the rate at which these substances are being discovered and characterized, it would not be surprising if there turned out to be several hundred different peptides conveying information at synapses in different subsets of neurons.

As we discussed in Chapter 3, neurotransmitters affect their targets by interacting with **receptors**, protein molecules embedded in the postsynaptic membrane that recognize the transmitter. The transmitter molecule binds to the receptor, changing its shape to open an ion channel (fast, **ionotropic** receptors), or altering chemical reactions within the target cell (slow, **metabotropic** receptors) (see Figure 3.13). Receptors add to the complexity of neural signaling because any given transmitter may bind to a wide variety of receptor types. The different **receptor subtypes** may trigger very different responses in target cells, and they also often have different anatomical distributions within the nervous system (**Figure 4.1**). As we will see shortly, drug development capitalizes on the existence of receptor subtypes. Although a given neurotransmitter will interact with all of the subtypes of its receptors, it is possible to design drugs that selectively affect

amine neurotransmitter A neurotransmitter based on modifications of a single amino acid nucleus, such as acetylcholine, serotonin, or dopamine.

amino acid neurotransmitter A neurotransmitter that is itself an amino acid, such as GABA, glycine, or glutamate.

peptide neurotransmitter A neurotransmitter consisting of a short chain of amino acids.

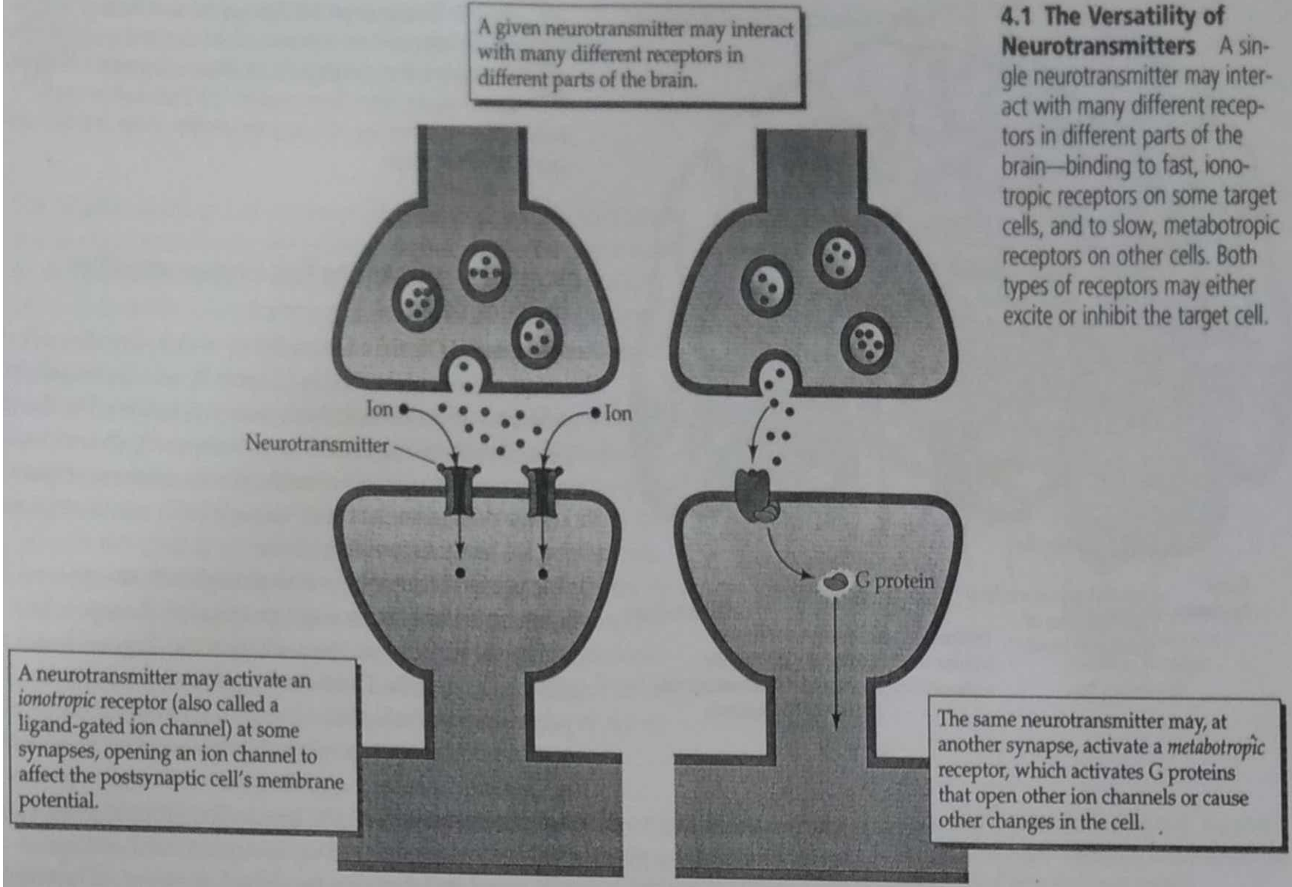
gas neurotransmitter A soluble gas, such as nitric oxide or carbon monoxide, that is produced and released by a neuron to alter the functioning of another neuron.

receptor Also called *receptor molecule*. A protein that captures and reacts to molecules of a transmitter or hormone.

ionotropic receptor A receptor protein that includes an ion channel that is opened when the receptor is bound by an agonist.

metabotropic receptor A type of transmitter receptor that does not contain an ion channel but may, when activated, use a G protein system to open a nearby ion channel.

receptor subtype Any type of receptor having functional characteristics that distinguish it from other types of receptors for the same neurotransmitter.



A given neurotransmitter may interact with many different receptors in different parts of the brain.

A neurotransmitter may activate an *ionotropic* receptor (also called a ligand-gated ion channel) at some synapses, opening an ion channel to affect the postsynaptic cell's membrane potential.

The same neurotransmitter may, at another synapse, activate a *metabotropic* receptor, which activates G proteins that open other ion channels or cause other changes in the cell.

4.1 The Versatility of Neurotransmitters A single neurotransmitter may interact with many different receptors in different parts of the brain—binding to fast, ionotropic receptors on some target cells, and to slow, metabotropic receptors on other cells. Both types of receptors may either excite or inhibit the target cell.

only one of the subtypes, thereby producing the specific effects associated with that receptor subtype.

A substance that binds to a receptor is termed a **ligand** and typically has one of three effects:

1. When bound to a receptor, a ligand classified as an **agonist** initiates the normal effects of the receptor.
2. A receptor **antagonist** is a ligand that binds to a receptor and does *not* activate it, thereby blocking it from being activated by other ligands.
3. An **inverse agonist**—a less common type of ligand—binds to the receptor and initiates an effect that is the *reverse* of the normal function of the receptor.

First we will look at some of the substances that the brain itself produces, which we classify as *endogenous ligands* (the word **endogenous** means "occurring naturally within the body"). We will then turn to the major categories of drugs that affect the brain (drugs are **exogenous** substances; that is, they are introduced from outside the body).

Neurotransmitter Systems Form a Complex Array in the Brain

The neurochemical complexity of the brain has become more evident as techniques such as immunocytochemistry (see Box 2.1) have provided a more complete appreciation of the location of these substances within the nervous system, and the multiplicity of ways in which they interact. Although at one time it was thought that each nerve cell contained only one transmitter, we now know that some nerve cells contain more than one—a phenomenon known as neurotransmitter **co-localization** or *co-release*. In this section we discuss the distribution of a few of the major neurotransmitters, and their receptors.

ligand A substance that binds to receptor molecules, such as those at the surface of the cell.

agonist A molecule, usually a drug, that binds a receptor molecule and initiates a response like that of another molecule, usually a neurotransmitter.

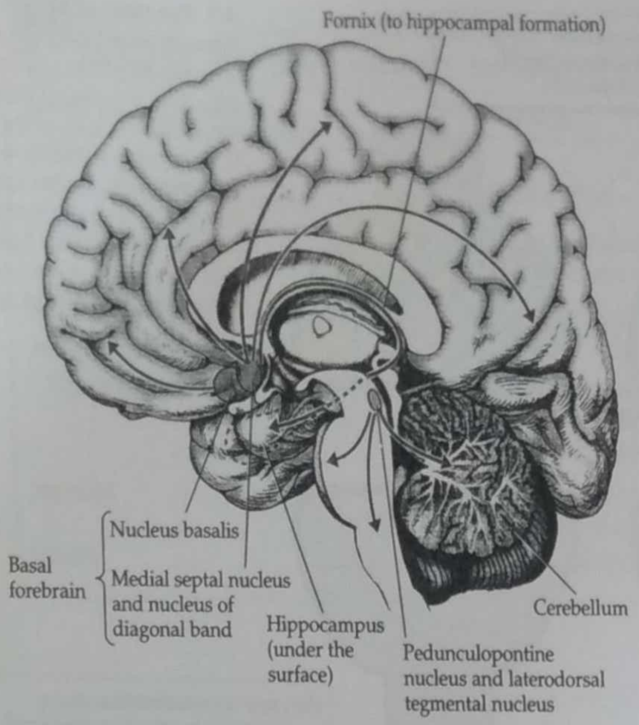
antagonist A molecule, usually a drug, that interferes with or prevents the action of a transmitter.

inverse agonist A substance that binds to a receptor and causes it to do the opposite of what the naturally occurring transmitter does.

endogenous Produced inside the body.

exogenous Arising from outside the body.

co-localization Also called *co-release*. Here, the appearance of more than one neurotransmitter in a given presynaptic terminal.


Fornix (to hippocampal formation)
Nucleus basalis
Basal forebrain
Medial septal nucleus and nucleus of diagonal band
Hippocampus (under the surface)
Pedunculopontine nucleus and laterodorsal tegmental nucleus
Cerebellum

4.2 Cholinergic Pathways in the Brain In this midsagittal view, the brain nuclei containing cell bodies of neurons that release ACh are shown in green; the projections of axons from these neurons are indicated by green arrows. Because they use ACh as a transmitter, these neurons are said to be *cholinergic*.

Acetylcholine was the first neurotransmitter to be identified

Acetylcholine (ACh), the chemical at work in Otto Loewi's classic experiment (described in Chapter 3), was the first chemical substance to be identified as a neurotransmitter. The distribution of ACh in the brain was subsequently determined by mapping of the enzymes involved in its synthesis; **Figure 4.2** shows the distribution of **cholinergic** (ACh-containing) nerve cell bodies and their projections.

Several distinct clusters of cholinergic cells are apparent. The basal forebrain includes major groups of cholinergic cells in the medial septal nucleus, the nucleus of the diagonal band, and the nucleus basalis. These cholinergic cells project to the hippocampus and amygdala, as well as throughout the cerebral cortex. Widespread loss of cholinergic neurons is evident in Alzheimer's disease, suggesting that cholinergic systems are crucial for learning and memory. Similarly, the cholinergic antagonist scopolamine interferes with learning and memory in experimental settings.

In Chapter 3 we noted that there are two broad classes of ACh receptors in the peripheral and central nervous systems: **nicotinic** and **muscarinic** receptors. Within each of these two groups are subtypes of receptors. Most nicotinic receptors are ionotropic, responding rapidly and usually having an excitatory effect. Muscles also use nicotinic ACh receptors, so antagonists, such as the drug curare, cause widespread paralysis. Muscarinic ACh receptors are G protein–coupled (metabotropic) receptors, so they have slower responses when activated, and they can be either excitatory or inhibitory (see Figure 3.13*b*). Muscarinic receptors can be blocked by the drugs atropine or scopolamine, producing pronounced changes in cognition.

Five monoamines act as neurotransmitters

There are two principal classes of monoamines: catecholamines and indoleamines. The **catecholamine** neurotransmitters are dopamine, epinephrine, and norepinephrine. The **indoleamines** are melatonin and serotonin. In the sections that follow, we will take a closer look at three important monoamines: dopamine, norepinephrine, and serotonin. (To learn more about the neuronal synthesis of the monoamines and ACh, see **A Step Further: Pathways for Neurotransmitter Synthesis** on the website.)

DOPAMINE About a million nerve cells in the human brain contain **dopamine (DA)**. **Figure 4.3** shows the locations of these cells and their projections in the brain. Several subtypes of DA receptors have been discovered and have been labeled D_1, D_2, D_3, D_4, and D_5, numbered in the order of their discovery. Dopaminergic neurons are found in several main groups; Figure 4.3 focuses on two of these groups: the **mesostriatal pathway** and the **mesolimbocortical pathway**.

The mesostriatal pathway, as the name indicates, originates from the mesencephalon (midbrain)—specifically the **substantia nigra** and nearby areas—and ascends as part of the medial forebrain bundle to innervate the **striatum**:

acetylcholine (ACh) An amine transmitter that stimulates muscle contraction, but is also found throughout the brain.

cholinergic Referring to cells that use acetylcholine as their synaptic transmitter.

nicotinic Referring to cholinergic receptors that respond to nicotine as well as to acetylcholine.

muscarinic Referring to cholinergic receptors that respond to the chemical muscarine as well as to acetylcholine.

catecholamines A class of monoamines that serve as neurotransmitters, including dopamine and norepinephrine.

indoleamines A class of monoamines that serve as neurotransmitters, including serotonin and melatonin.

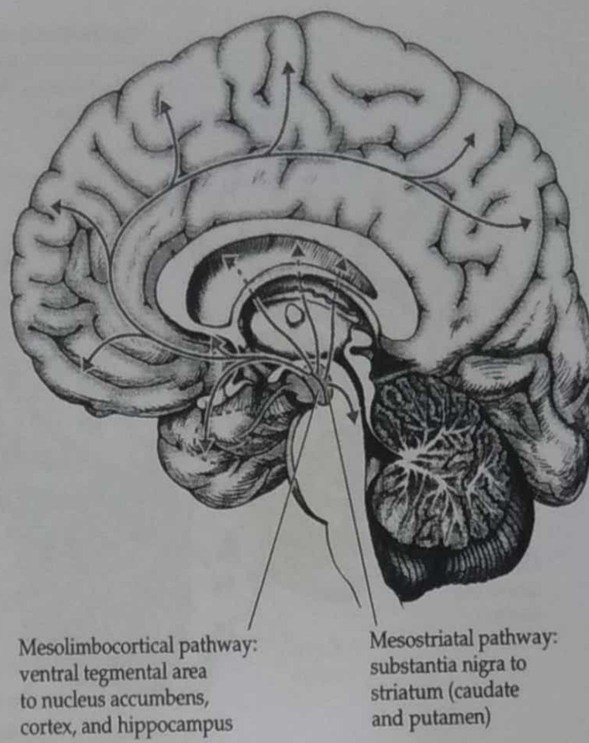
dopamine (DA) A monoamine transmitter found in the midbrain—especially the substantia nigra—and basal forebrain.

mesostriatal pathway A set of dopaminergic axons arising from the midbrain and innervating the basal ganglia, including those from the substantia nigra to the striatum.

mesolimbocortical pathway A set of dopaminergic axons arising in the midbrain and innervating the limbic system and cortex.

substantia nigra A midbrain structure that provides dopaminergic projections to areas of the forebrain, especially the basal ganglia.

striatum The caudate nucleus and putamen together.



4.3 Dopaminergic Pathways in the Brain The neurons in the pathways represented in this midsagittal view release dopamine and thus are called *dopaminergic*.

the caudate nucleus and putamen (see Figure 4.3). Although this group contains relatively few nerve cells, a single axon can give rise to thousands of synapses. The mesostriatal DA pathway plays a crucial role in motor control, and significant loss of these neurons produces the movement problems of Parkinson's disease (described in Chapter 11).

The mesolimbocortical pathway also originates in the midbrain, in the **ventral tegmental area (VTA)** (see Figure 4.3), and projects to the limbic system (amygdala, nucleus accumbens, hippocampus) and the cortex. A rich research literature (e.g., Nader et al., 1997) implicates this system, especially via the dopamine D_2 receptor subtype, in reward and reinforcement; we revisit this topic at the end of the chapter. In humans, dopamine released from mesolimbocortical neurons in the amygdala appears to participate in the performance of specific cognitive functions, such as verbal learning (Fried et al., 2001). Abnormalities in the mesolimbocortical pathway are associated with some of the symptoms of schizophrenia.

NOREPINEPHRINE Neurons that release **norepinephrine (NE)** are organized into three main clusters in the brainstem: the **locus coeruleus** in the pons, the lateral tegmental system of the midbrain, and the dorsal medullary group (**Figure 4.4**). Because norepinephrine is also known as *noradrenaline*, NE-producing cells are said to be **noradrenergic**.

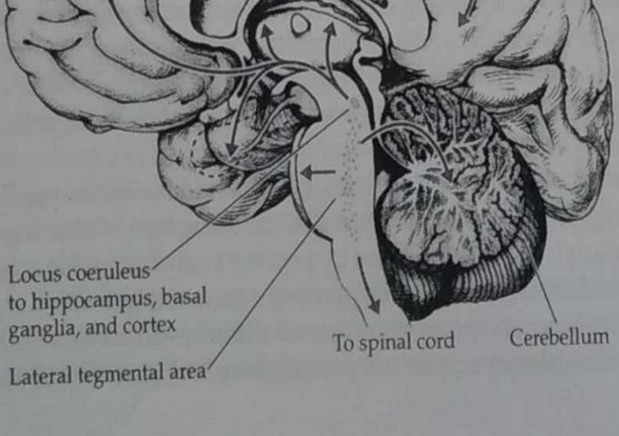
Fibers from the noradrenergic cells of the locus coeruleus project broadly throughout the cerebrum, including the cerebral cortex, limbic system, and thalamic nuclei. In addition, the cerebellum and spinal cord receive noradrenergic innervation. The CNS contains four subtypes of NE receptors—α_1-, α_2-, β_1-, and β_2-adrenoceptors—all of which are metabotropic receptors. Because of their wide projections, noradrenergic systems are believed to modulate many behavioral and physiological processes, including mood, overall arousal, and sexual behavior.

ventral tegmental area (VTA) A portion of the midbrain that projects dopaminergic fibers to the nucleus accumbens.

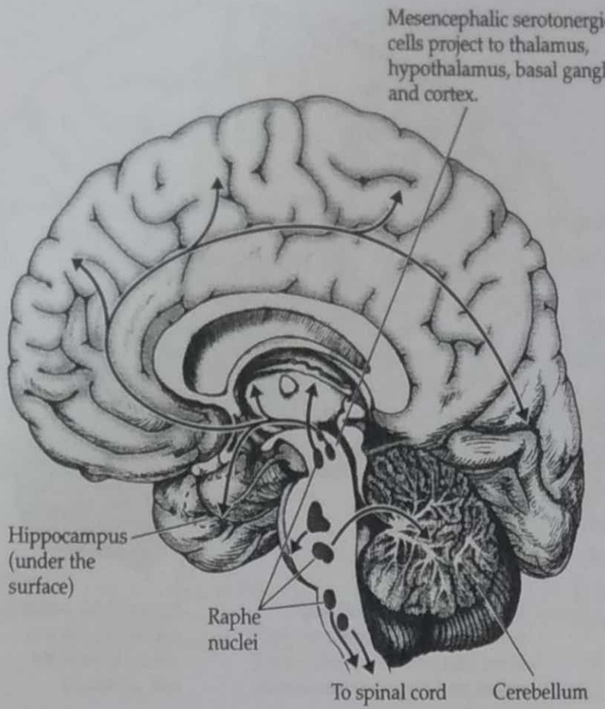
norepinephrine (NE) Also called *noradrenaline*. A synaptic transmitter that is produced mainly in brainstem nuclei.

locus coeruleus A small nucleus in the brainstem whose neurons produce norepinephrine and modulate large areas of the forebrain.

noradrenergic Referring to systems using norepinephrine (noradrenaline) as a transmitter.



4.4 Noradrenergic Pathways in the Brain The neurons in the pathways shown in this midsagittal view release norepinephrine (noradrenaline) as a transmitter and thus are said to be *noradrenergic*.


Mesencephalic serotonergic cells project to thalamus, hypothalamus, basal ganglia, and cortex.
Hippocampus (under the surface)
Raphe nuclei
To spinal cord
Cerebellum

4.5 Serotonergic Pathways in the Brain The neurons in the nuclei shown in this midsagittal view release serotonin (5-HT) and thus are said to be *serotonergic*.

SEROTONIN Because its chemical name is 5-hydroxytryptamine, **serotonin** is abbreviated **5-HT**. Large areas of the brain are innervated by **serotonergic** fibers, although 5-HT cell bodies are relatively few and are concentrated along the midline in the **raphe nuclei** (pronounced "ra-FAY"; Latin for "seam") of the midbrain and brainstem. **Figure 4.5** shows the distribution of serotonergic cell bodies and their fiber projections. Only about 200,000 of the 100 billion neurons of the human brain are serotonergic, but they exert widespread influence through the rest of the brain, especially the projection emanating from the **dorsal raphe**.

Serotonin has been implicated in the control of sleep states (see Chapter 14), mood, sexual behavior, anxiety, and many other functions. Drugs that globally increase 5-HT activity are effective antidepressants; Prozac is an example (see Chapter 16). At least 15 types of 5-HT receptors (5HT$_1$, 5HT$_2$, and so on) have been described, and the effects of serotonergic drugs on behavior often depend on which subtypes of 5-HT receptors are affected (e.g., Gorzalka et al., 1990; Miczek et al., 2002).

Some amino acids act as neurotransmitters

The most common transmitters in the brain are based on amino acids. **Glutamate** and **aspartate** are important excitatory neurotransmitters. **Gamma-aminobutyric acid** (**GABA**) and **glycine** are major inhibitory transmitters. These transmitters are distributed throughout the central nervous system.

Glutamatergic transmission employs *AMPA, kainate,* and *NMDA* receptors (their names refer to drugs that act as selective agonists). Because NMDA-type glutamate receptors are active in a fascinating model of learning and memory, they have been studied very closely. This topic is discussed more fully in Chapter 18, and the details of the unique behavior of NMDA receptors are provided on the website in **A Step Further: A Receptor with a Long Memory**. There are also several metabotropic glutamate receptors (mGluR's), which act more slowly because they work through second messengers.

Glutamate is associated with **excitotoxicity**, a phenomenon in which neural injury, such as a stroke or trauma, provokes an excessive release of glutamate that produces prolonged depolarization of postsynaptic cells. This overexcitation ultimately kills the postsynaptic neurons, exacerbating the effects of the brain injury. Another interesting feature of glutamatergic synapses is that nearby astrocytes seem to be responsible for taking up glutamate, clearing it from the cleft after synaptic transmission (Rothstein, 2000).

GABA receptors are divided into large classes designated *GABA$_A$*, *GABA$_B$*, and *GABA$_C$* receptors. Although they all show affinity for GABA, the subtypes of receptors exhibit quite different properties.

GABA$_A$ receptors are ionotropic (they are ligand-gated chloride channels; see Figure 4.1), and when activated they produce fast inhibitory postsynaptic potentials. Each GABA$_A$ receptor is made up of five protein subunits surrounding a Cl^- ion channel that can be widened or narrowed depending on the state of the surrounding complex. By mixing and matching of the various protein subunits that make them up, the brain may in fact produce dozens of different kinds of GABA$_A$ receptors, offering binding sites to at least 14 different types of substances, in addition to GABA (Darlison et al., 2005; Johnston, 1996, 2005).

GABA$_B$ receptors are metabotropic receptors, in contrast to the ionotropic GABA$_A$ receptors. GABA$_B$ receptors are associated with a slow-occurring type of inhibitory postsynaptic potential, which is probably mediated by a special kind of interneuron called a *neurogliaform cell* (Tamás et al., 2003). GABA$_C$ receptors are ionotropic with a chloride channel, but they differ in certain details of their subunit structure from other GABA receptors. Given GABA's inhibitory actions, it is not surprising that some GABA agonists

serotonin (5-HT) A synaptic transmitter that is produced in the raphe nuclei and is active in structures throughout the cerebral hemispheres.

serotonergic Referring to neurons that use serotonin as their synaptic transmitter.

raphe nuclei A string of nuclei in the midline of the midbrain and brainstem that contain most of the serotonergic neurons of the brain.

dorsal raphe One of the midbrain nuclei that give rise to most of the serotonergic projections of the brain.

glutamate An amino acid transmitter, the most common excitatory transmitter.

aspartate An amino acid transmitter that is excitatory at many synapses.

gamma-aminobutyric acid (GABA) A widely distributed amino-acid transmitter, and the main inhibitory transmitter in the mammalian nervous system.

glycine An amino acid transmitter, often inhibitory.

glutamatergic Referring to cells that use glutamate as their synaptic transmitter.

excitotoxicity The property by which neurons die when overstimulated, as with large amounts of glutamate.

are potent tranquilizers (e.g., Valium), and that inverse agonists of GABA receptors can provoke seizures by decreasing the important inhibitory influence of GABA.

Many peptides function as neurotransmitters

Many different peptides are found in the brain; those that have a prominent role as neurotransmitters include

1. **Opioid peptides** (peptides that can mimic opiate drugs such as morphine), including met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin;
2. A group of peptides found in the gut and spinal cord or brain, including substance P, cholecystokinin (CCK), neurotensin, neuropeptide Y (NPY), and others;
3. Pituitary hormones such as oxytocin and vasopressin, among others.

Many of these peptides act as neurotransmitters at certain synapses, but they also act as hormones in other systems (see Chapter 5). Peptide transmitters are often co-localized with other neurotransmitters, especially monoamines.

Some neurotransmitters are gases

It may surprise you to learn that neurons use certain gas molecules that dissolve in water (and so are called *soluble gases*) to communicate information. The best studied of these is **nitric oxide**, or **NO** (distinct from *nitrous* oxide, or laughing gas, which is N_2O). The actions of gas neurotransmitters like NO are different from those of the classic transmitters in several important ways. First, nitric oxide is produced in cellular locations other than the axon terminals, especially the dendrites, and molecules of nitric oxide are not held in or released from vesicles; the substance simply diffuses out of the neuron as soon as it is produced. Second, the released NO doesn't interact with membrane-bound receptors on the surface of the target cell, but rather it diffuses into the target cell and stimulates production of the second messenger cyclic GMP (cGMP). And third, NO serves as a **retrograde transmitter**: it diffuses from the postsynaptic neuron back to the presynaptic neuron, where it stimulates changes in synaptic efficacy that may be involved in learning and memory (this topic is covered in more detail in Chapter 18). Found widely throughout the body, NO has been implicated in processes as diverse as hair growth and penile erection (Burnett, 2006), in addition to its role in the brain.

Research on Drugs Ranges from Molecular Processes to Effects on Behavior

In everyday English, we use the term *drug* in different ways. One common meaning is "a medicine used in the treatment of a disease" (as in *prescription drug* or *over-the-counter drug*). Quite a different meaning of *drug*, but also a common one, is "a psychoactive agent," especially an addictive one—that is, a drug of abuse. The common element of these meanings is a substance that, taken in relatively small amounts, has clear effects on experience, mood, emotion, activity, and/or health.

Some drugs originally evolved in plants, often as a defense against being eaten. Other modern drugs are synthetic (human-made) and tuned to affect specific transmitter systems. To understand how drugs work, we must use many levels of analysis—from molecules to anatomical systems to behavioral effects and experiences.

Drugs fit like keys into molecular locks

Some drugs are effective because they interact with lipid molecules that make up the membrane, or because they directly alter the activity of particular enzymes, but most drugs of interest to biological psychology are ligands that interact with specific receptor molecules. These receptors may be located either in the cell membrane or in the interior of the neuron.

Recall that any given neurotransmitter interacts with a variety of different subtypes of receptors. This principle is crucial to neuropharmacology because, unlike the transmitter, which will act on all its receptor subtypes, a drug can be targeted to interact with

opioid peptide A type of endogenous peptide that mimics the effects of morphine in binding to opioid receptors and producing marked analgesia and reward.

nitric oxide (NO) A soluble gas that serves as a retrograde gas neurotransmitter in the nervous system.

retrograde transmitter A neurotransmitter that diffuses from the postsynaptic neuron back to the presynaptic neuron.

binding affinity The propensity of molecules of a drug (or other ligand) to bind to their corresponding receptors. Drugs with high affinity for their receptors are effective even at low doses.

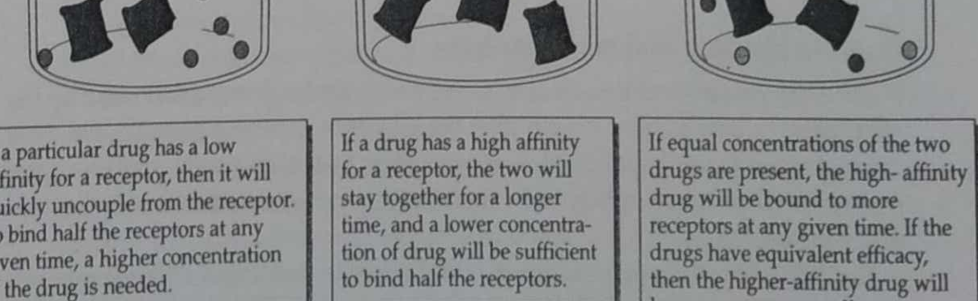
just one or a few receptor subtypes. The various subtypes of receptors for a transmitter generally differ in their distribution within the brain, and they also serve very different cellular functions, so selectively activating or blocking specific subtypes of receptors can have widely varying effects. For example, treating someone with doses of serotonin would activate all of her serotonin receptors, regardless of subtype, and produce a variety of nonspecific effects. But drugs that are selective antagonists of 5-HT_3 receptors, showing little activity at other subtypes of serotonin receptors, produce a powerful and specific anti-nausea effect. We have also discussed how a single transmitter, GABA, may act on hundreds of different receptors. Apparently evolution tinkers with the structure of receptors more than transmitters.

Drug molecules do not seek out particular receptor molecules; rather, drug molecules spread widely throughout the body, and when they come in contact with receptor molecules possessing the specific shape that fits the drug molecule, the two molecules bind together briefly and begin a chain of events. The lock-and-key analogy is often used for this binding action, as mentioned in Chapter 3. In the case of receptor-selective drugs, though, we have to think of keys (drug molecules) trying to insert themselves in all the locks (receptor molecules) in the neighborhood; each such key fits into only a particular subset of the locks. Once the drug (the key) binds to the receptor (the lock), it alters the activity of the receptor, activating it or blocking it. But the binding is usually temporary, and when the drug or transmitter breaks away from the receptor, the receptor resumes its unbound shape and functioning.

Drug–receptor interactions vary in specificity and activity

The tuning of drug molecules to receptors is not absolutely specific. That is, a particular drug molecule will generally bind strongly to one kind of receptor, more weakly to some other types, and not at all to many others. A drug molecule that has more than one kind of action in the body exhibits this flexibility because it affects more than one kind of receptor molecule. For example, some drugs combat anxiety at low doses without producing sedation (relaxation, drowsiness), but at higher doses they cause sedation, probably because at those doses they activate additional types of receptors.

The degree of chemical attraction between a ligand and a receptor is termed **binding affinity** (or simply **affinity**). A drug with high affinity for a particular type of receptor will selectively bind to that type of receptor even at low doses, and will stay bound for a relatively long time. Lower-affinity receptors will attract and bind fewer molecules of the drug. **Figure 4.6** illustrates the measurement of binding affinity.

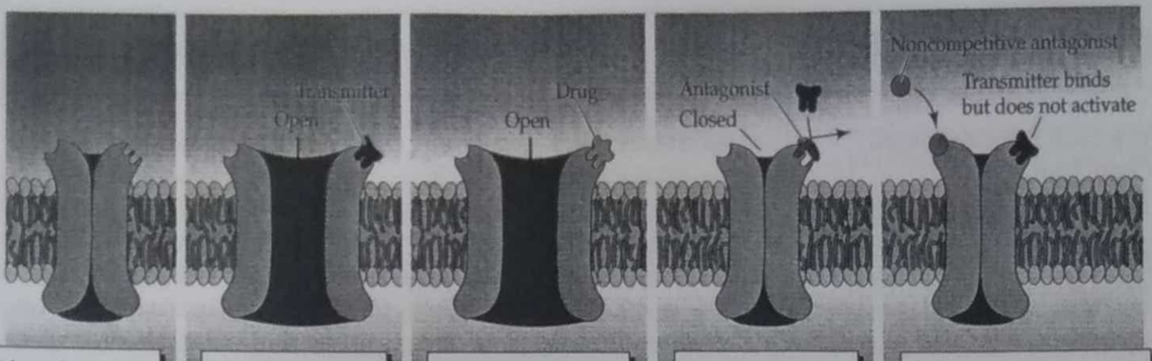


If a particular drug has a low affinity for a receptor, then it will quickly uncouple from the receptor. To bind half the receptors at any given time, a higher concentration of the drug is needed.

If a drug has a high affinity for a receptor, the two will stay together for a longer time, and a lower concentration of drug will be sufficient to bind half the receptors.

If equal concentrations of the two drugs are present, the high-affinity drug will be bound to more receptors at any given time. If the drugs have equivalent efficacy, then the higher-affinity drug will have a more potent effect.

4.6 Using Binding Affinity to Compare Drug Effectiveness


Transmitter
Open
Drug
Open
Antagonist
Closed
Noncompetitive antagonist
Transmitter binds but does not activate

Unbound receptor. In this example, it is normally closed.

An endogenous ligand is a naturally occurring molecule, such as a transmitter, that binds to the receptor. An endogenous ligand usually activates its cognate receptor and is therefore classified as an **agonist.**

An exogenous ligand (that is, a drug or toxin) that resembles the endogenous ligand and is capable of binding to the receptor and activating it is classified as a **receptor agonist.**

Some substances bin to receptors but do not activate them, and simply block agonists from binding to the receptors. These are classified as **competitive antagonists.**

Some agonist or antagonist drugs may bind to target receptors at a site that is *different* from where the endogenous ligand binds; such drugs are know as **noncompetitive agonists or antagonists.**

4.7 The Agonistic and Antagonistic Actions of Drugs

Once bound, the propensity of a ligand to *activate* the receptor to which it is bound is termed its **efficacy** (or **intrinsic activity**). As you might guess, agonists have high efficacy and antagonists have low efficacy (**Figure 4.7**). **Partial agonists** are drugs that produce a middling response regardless of dose. So it is a combination of affinity and efficacy—where it binds and what it does—that determines the overall action of a drug. To some extent we can compare the effectiveness of different drugs by comparing their affinity for the receptor of interest (see Figure 16.9 for an example).

So far we have been talking about drugs that are **competitive ligands**: drugs that bind to the same receptor sites as the endogenous transmitter. To complicate things a bit further, some drugs bind to a part of the receptor complex that does not normally bind the transmitter (see Figure 4.7). In such cases the drug does not directly compete with the transmitter for its binding site, so we say that the drug is a **noncompetitive ligand**, binding to a **modulatory site** on the receptor. Noncompetitive ligands may either activate the receptor, thereby acting as noncompetitive agonists, or prevent the receptor from being activated by the transmitter, thus acting as noncompetitive antagonists. We'll discuss modulatory sites on the GABA receptor later in this chapter.

Dose–response relationships reflect the potency and safety of drugs

As you would probably guess, administering larger doses of a drug ultimately increases the proportion of receptors that are bound and affected by the drug. Within certain limits, this increase in receptor binding also increases the response to the drug; in other words, greater doses tend to produce greater effects. When plotted as a graph, the relationship between drug doses and observed effects is called a **dose–response curve** (**DRC**). Careful analysis of DRCs reveals many aspects of a drug's activity and is one of the main tools for understanding **pharmacodynamics** (the functional relationships between drugs and their targets).

Box 4.1 illustrates how DRCs are used to assess many important characteristics of drugs. For example, the DRC reveals the effective dose range of a drug, allows comparison of the potencies of different drugs, and gives us a clear indication of the range of doses of a drug that are safe to use. The DRC can also help us predict the dose level at which the risk of side effects emerges.

efficacy or intrinsic activity The extent to which a drug activates a response when it binds to a receptor.

partial agonist or partial antagonist A drug that, when bound to a receptor, has less effect than the endogenous ligand would.

competitive ligand A substance that directly competes with the endogenous ligand for binding to a receptor molecule.

noncompetitive ligand A drug that affects a transmitter receptor while binding at a site other than that bound by the endogenous ligand.

modulatory site A portion of a receptor that, when bound by a compound, alters the receptor's response to its transmitter.

dose–response curve (DRC) A formal plot of a drug's effects (on the *y*-axis) versus the dose given (on the *x*-axis).

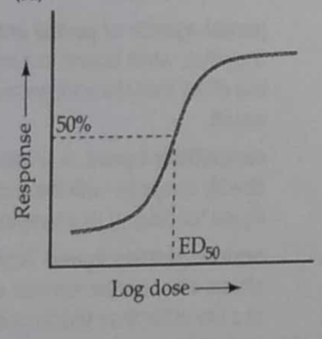
pharmacodynamics Collective name for the factors that affect the relationship between a drug and its target receptors, such as affinity and efficacy.

BOX 4.1 Mind the Curves

The Basic Dose–Response Curve (DRC)

The DRC is a fairly simple graph. Increasing doses of the test drug are plotted along the *x*-axis (by convention a logarithmic scale is used), and increasing response strength is ordered along the *y*-axis. For most drugs, and most responses, the DRC has the characteristic slanted S shape shown in Figure A. This shape arises because at very low doses too little drug is available to provoke a measurable response, and at higher doses sufficient high-affinity receptors are bound that adding more drug cannot provoke any further response; this is termed the **maximal response**. At *very* high doses, most of the receptors are occupied, and we say that the receptors are **saturated**. Note that maximal response and saturation are not the same thing; a maximal response to a drug is often reached before the receptors are saturated. The slanted middle portion of the curve therefore corresponds to the range of potentially useful doses. The dose at which the drug has a half-maximal response is termed the **ED_{50}** (for *effective dose 50%*) and is used for comparing different drugs.

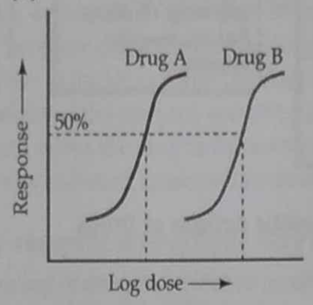
(A)



Relative Potency

The **relative potencies** of two drugs can be directly assessed by comparison of their ED_{50} values. In the example shown in Figure B, both test drugs have comparable effects, but drug A has the effects at substantially lower doses and is thus more potent than drug B. This sort of analysis is useful for comparing chemically related drugs, or *congeners*.

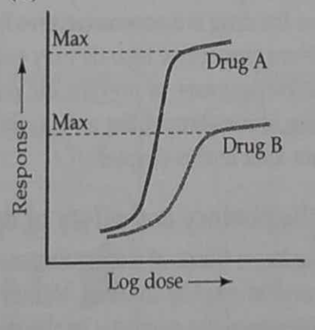
(B)



Drug Efficacy

The evaluation of **drug efficacy** is based on maximal responses rather than doses. In Figure C, drug A has a much greater maximal effect than drug B, no matter what dose of drug B is used. A drug that has only moderate efficacy is termed a *partial agonist* (or, equivalently, a *partial antagonist*).

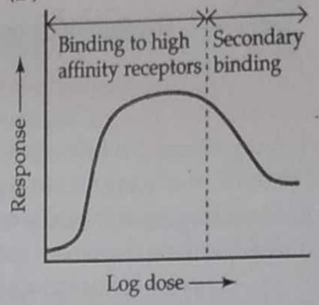
(C)



Secondary Binding

What happens if we add very high doses to the dose–response relationship? Often the result will be a *nonmonotonic* DRC (Figure D), which is normal up to a point but then reverses. The measured response begins to fluctuate (or new and perhaps unwanted responses appear) with further increases in dose. At that point, the drug has reached sufficiently high concentrations in the body that it has saturated all of its highest-affinity sites and is starting to exert effects elsewhere, through secondary binding to lower-affinity sites.

(D)



Therapeutic Index

The **therapeutic index** of a drug is a measure of its safety, expressed as the separation between useful doses and toxic doses. Classically it is defined by comparison of a drug's ED_{50} with the dose at which half of treated animals will die (termed the *lethal dose 50%* or **LD_{50}**). Because LD_{50} studies are controversial, methods have been developed to estimate LD_{50} with less actual lethality. For example, testing for *TD_{50}* (the dose at which toxic reactions first begin

Repeated treatments can reduce the effectiveness of drugs

Our bodies are impressively adaptable. Many body systems change their functioning in order to accommodate environmental challenges, and in most ways drug treatments can be viewed as changes in the body's chemical environment. This adaptability is evident in the development of drug **tolerance**, in which successive treatments with a particular drug have decreasing effects.

tolerance A condition in which, with repeated exposure to a drug, an individual becomes less responsive to a constant dose.

BOX 4.1 (continued)

to appear in 50% of treated animals) provides a satisfactory substitute in many cases.

In the examples shown in Figure E, drug A (in blue) exhibits a wide therapeutic index: its ED_{50} and LD_{50} values are far apart, and the drug is considered to be relatively safe. Drug B (in yellow) is much more dangerous, because its ED_{50} and LD_{50} are close together and the risk of accidentally giving a lethal dose is high. In fact, the slight overlap of the two curves indicates that a dose that is effective in some individuals could be lethal in others.

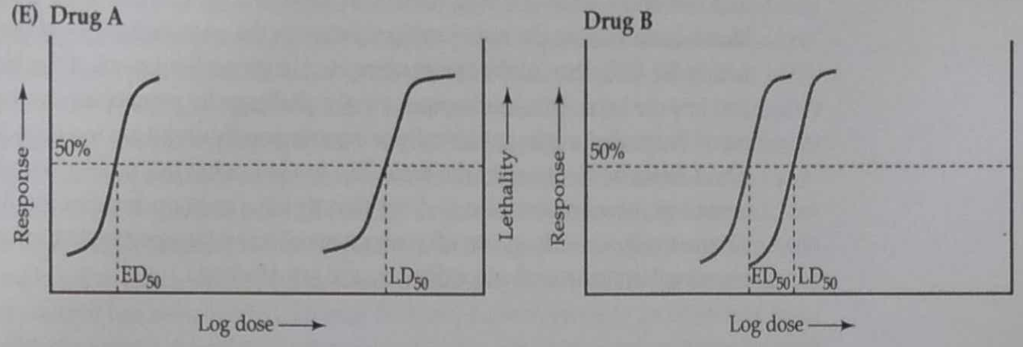
The issue of drug safety is especially critical with respect to substance abuse, where doses are not established by medical guidelines. The median lethal dose of marijuana is more than 1000 times the recreational dose, so it resembles drug A in this example, but some drugs, like heroin and (perhaps surprisingly) alcohol, have an LD_{50} that is only 5 to 10 times the recreational dose, more like drug B (Gable, 2006). This explains why overdose is so much more common with these substances.

maximal response The strongest effect that a drug can have on a particular measured response, no matter how much of the drug is given.

saturated Referring to the condition in which a maximal number of receptors of one type have been bound by molecules of a drug; additional doses of drug cannot produce additional binding.

ED_{50} Effective dose 50%; the dose of a drug that is required to produce half of its maximal effect.

LD_{50} Lethal dose 50%; the dose of a drug at which half the treated animals will die.



Drug tolerance can develop in several different ways. Some drugs provoke **metabolic tolerance**, in which the body's metabolic organ systems (such as the liver) become increasingly effective at eliminating the drug before it has a chance to affect the brain (or other target).

Alternatively, the target tissue itself may show altered sensitivity to the drug, or **functional tolerance**. In neuropharmacology, an important source of functional tolerance is the regulation of receptor proteins—changing the number of receptors present in the cell membrane. This receptor regulation alters neuronal sensitivity in the direction opposite to the drug's effect. Thus, over the course of repeated exposures to an *agonist* drug, target neurons often **down-regulate** (decrease the available receptors to which the drug can bind), thereby countering the drug effect. If the drug is an *antagonist*, target neurons may instead **up-regulate** (increase the number of receptors). Tolerance to a drug often generalizes to other drugs belonging to the same chemical class; this effect is termed **cross-tolerance**. For example, people who have developed tolerance to morphine tend to exhibit a degree of tolerance to all the other drugs in the opiate category, including codeine, heroin, and methadone. For drugs that have multiple effects in the body, tolerance to the various effects may develop at different rates.

Once established, drug tolerance is believed to be a major cause of **withdrawal symptoms**, the unpleasant sensations associated with cessation of drug use, while neural systems reregulate. As we will discuss later, many researchers believe that avoidance of the physical discomfort of withdrawal symptoms is an important aspect of drug addiction. Furthermore, some drug responses can become *stronger* with repeated treatments, rather

metabolic tolerance The form of drug tolerance that arises when the metabolic machinery of the body becomes more efficient at clearing the drug, as a consequence of repeated exposure.

functional tolerance Decreased responding to a drug after repeated exposures, generally as a consequence of up- or down-regulation of receptors.

down-regulation A compensatory reduction in receptor availability at the synapses of a neuron.

up-regulation A compensatory increase in receptor availability at the synapses of a neuron.

cross-tolerance A condition in which the development of tolerance for an administered drug causes an individual to develop tolerance for another drug.

withdrawal symptom An uncomfortable symptom that arises when a person stops taking a drug that he or she has used frequently, especially at high doses.

sensitization A process in which the body shows an enhanced response to a given drug after repeated doses.

bioavailable Referring to a substance, usually a drug, that is present in the body in a form that is able to interact with physiological mechanisms.

biotransformation The process in which enzymes convert a drug into a metabolite that is itself active, possibly in ways that are substantially different from the actions of the original substance.

pharmacokinetics Collective name for all the factors that affect the movement of a drug into, through, and out of the body.

blood–brain barrier The mechanisms that make the movement of substances from capillaries into brain cells more difficult than exchanges in other body organs, thus affording the brain greater protection from exposure to some substances found in the blood.

than weaker. Termed **sensitization**, this effect is thought to contribute to the drug craving that addicts experience. This heightened sensitivity may last for a prolonged period, and it seems to reflect long-term brain changes in response to drugs of abuse (Peris et al., 1990).

Drugs are administered and eliminated in many different ways

The amount of drug that reaches the brain and the speed with which it starts acting are determined in part by the drug's route of administration. Some routes, such as smoking or intravenous injection, rapidly increase the concentration of drug in the body that is **bioavailable** (free to act on the target tissue, and therefore not bound to other proteins or in the process of being metabolized or excreted). With other routes, such as oral ingestion, the concentration of drug builds up more slowly over longer periods of time. Furthermore, the duration of a drug effect is largely determined by the manner in which the drug is metabolized and excreted from the body—via the kidneys, liver, lungs, and other routes. In some cases, the metabolites of drugs are themselves active; this **biotransformation** of drugs can be a source of unwanted side effects. Factors that affect the movement of a drug into, through, and out of the body are collectively referred to as **pharmacokinetics**.

Humans have devised a remarkable variety of techniques for introducing substances into the body; these are summarized in **Table 4.2**. In Chapter 2 we discussed the **blood–brain barrier**: the tight junctions between the endothelial cells of blood vessels within the CNS that inhibit the movement of larger molecules out of the bloodstream and into the brain. This barrier poses a major challenge for neuropharmacology because many drugs that might be clinically or experimentally useful are too large to pass the blood–brain barrier to enter the brain. To a limited extent this problem can be circumvented by the administration of drugs directly into the brain, but that is a drastic step. Alternatively, some drugs can take advantage of active transport systems that normally move nutrients out of the bloodstream and into the brain.

TABLE 4.2 The Relationship between Routes of Administration and Effects of Drugs

Route of administration	Examples and mechanisms	Typical speed of effects
INGESTION Tablets and capsules Syrups Infusions and teas Suppositories	Many sorts of drugs and remedies; depends on absorption by the gut, which is somewhat slower than most other routes	Slow to moderate
INHALATION Smoking Nasal absorption Inhaled powders and sprays	Nicotine, cocaine, and other drugs of abuse; also used for a variety of prescription drugs and hormone treatments. Inhalation methods take advantage of the rich vascularization of the nose and lungs to convey drugs directly into the bloodstream.	Moderate to fast
PERIPHERAL INJECTION Subcutaneous Intramuscular Intraperitoneal (abdominal) Intravenous	Many drugs; subcutaneous (under the skin) injections tend to have the slowest effects because they must diffuse into nearby tissue in order to reach the bloodstream; intravenous injections have very rapid effects because the drug is placed directly into circulation.	Moderate to very fast
CENTRAL INJECTION Intracerebroventricular (into ventricular system) Intrathecal (into spinal CSF) Epidural (under the dura mater) Intracerebral (directly into a brain region)	Central methods involve injection directly into the CNS; used in order to circumvent the blood–brain barrier, to rule out peripheral effects, or to directly affect a discrete brain location.	Fast to very fast

Drugs Affect Each Stage of Neural Conduction and Synaptic Transmission

The great majority of drugs that act on the nervous system to produce changes in behavior do so by altering synaptic function or neural conduction. **Figure 4.8** illustrates the principal synaptic processes that are targeted by CNS drugs. In the discussion that follows we'll comment on some of these agents and the general properties of the pharmacological categories to which they belong.

Drugs affect presynaptic events

Inhibition of axonal transport by a drug (e.g., colchicine has this activity) prevents enzymes and other key compounds that originate in the cell body from being replaced in the axon terminals. Because these supplies are needed to manufacture transmitter chemicals and vesicles, drugs that inhibit axonal transport prevent replenishment of the transmitter agent as it is used up, and synaptic transmission fails. The drug reserpine interferes with the storage of catecholamine transmitters in vesicles by making the vesicles leaky. And even if a presynaptic terminal has an adequate supply of transmitter stored in vesicles, various agents or conditions can prevent the release of transmitter when a nerve impulse reaches the terminal. Low extracellular calcium (Ca^{2+}) concentration, or pharmacological blockade of Ca^{2+} channels at the axon terminals, inhibits transmitter release by preventing the Ca^{2+} influx that is required for transmitter release.

Some toxins prevent the release of specific kinds of transmitters (de Paiva et al., 1993). For instance, botulinum toxin, which is formed by bacteria that multiply in improperly canned food, poisons many people each year by blocking the release of ACh. Botulinum toxin binds to specialized receptors in nicotinic cholinergic membranes and is transported into the cell, where it blocks the Ca^{2+}-dependent release of transmitter (McMahon et al., 1992), resulting in muscle paralysis. In much-diluted form, botulinum toxin is marketed as Botox, which inhibits facial wrinkling by locally paralyzing facial muscles into which it has been injected. Tetanus (lockjaw) bacteria produce an often fatal toxin that blocks activity at inhibitory synapses and causes strong involuntary contractions of muscles.

Other agents stimulate or facilitate the release of certain transmitters. **Neuromodulators** are not transmitters themselves; rather they affect either the release of the transmitter or the receptor response to the transmitter. Perhaps the most beloved of all neuromodulators is the **caffeine** that we obtain from drinking coffee and other caffeinated beverages (worldwide, we consume about 400 *billion* cups of coffee each year). Caffeine acts as an exogenous neuromodulator, by blocking the effect of an endogenous neuromodulator, **adenosine**. By competing with adenosine for access to adenosine A_{2A} receptors on the surfaces of neurons, caffeine produces long-lasting changes in an internal signaling pathway mediated by a protein called DARPP-32 (which, incredibly, is short for ***d****opamine- and cyclic* ***AMP****–****r****egulated* ***p****hospho****p****rotein of molecular mass* ***32****,000*) (Lindskog et al., 2002). Because adenosine normally acts on presynaptic terminals to inhibit the release of catecholamine transmitters, caffeine increases catecholamine release, causing arousal. (Interestingly, by a different route, the stimulant drug amphetamine also facilitates catecholamine release.)

Where does adenosine normally come from? At least some catecholaminergic synapses co-release adenosine with the neurotransmitter. The adenosine binds to receptors on the same presynaptic terminal that released it, so we say that the adenosine acts on **autoreceptors**. It may seem odd that a neuron that is releasing transmitter would also release a neuromodulator to inhibit transmitter release, but this type of complicated modulation of transmitter release is probably the rule, not the exception.

Drugs affect postsynaptic events

As we've discussed, postsynaptic receptor molecules can be blocked or activated by various drugs. For example, curare blocks nicotinic ACh receptors. Because the synapses

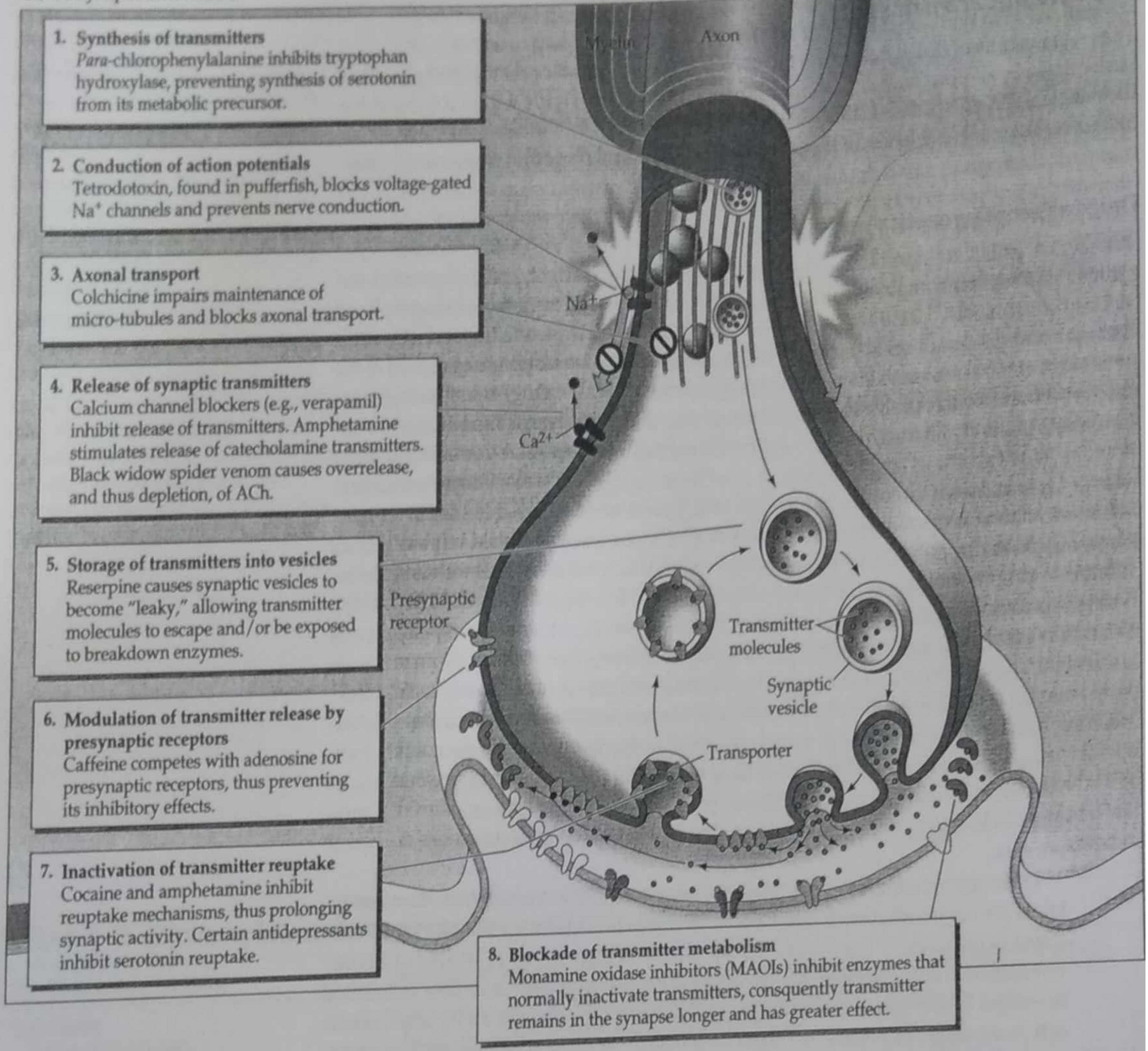
neuromodulator A substance that influences the activity of synaptic transmitters.

caffeine A stimulant compound found in coffee, cacao, and other plants.

adenosine In the context of neural transmission, a neuromodulator that alters synaptic activity.

autoreceptor A receptor for a synaptic transmitter that is located in the presynaptic membrane and tells the axon terminal how much transmitter has been released.

(*a*) **Presynaptic mechanisms**



1. **Synthesis of transmitters** *Para*-chlorophenylalanine inhibits tryptophan hydroxylase, preventing synthesis of serotonin from its metabolic precursor.

2. **Conduction of action potentials** Tetrodotoxin, found in pufferfish, blocks voltage-gated Na^+ channels and prevents nerve conduction.

3. **Axonal transport** Colchicine impairs maintenance of micro-tubules and blocks axonal transport.

4. **Release of synaptic transmitters** Calcium channel blockers (e.g., verapamil) inhibit release of transmitters. Amphetamine stimulates release of catecholamine transmitters. Black widow spider venom causes overrelease, and thus depletion, of ACh.

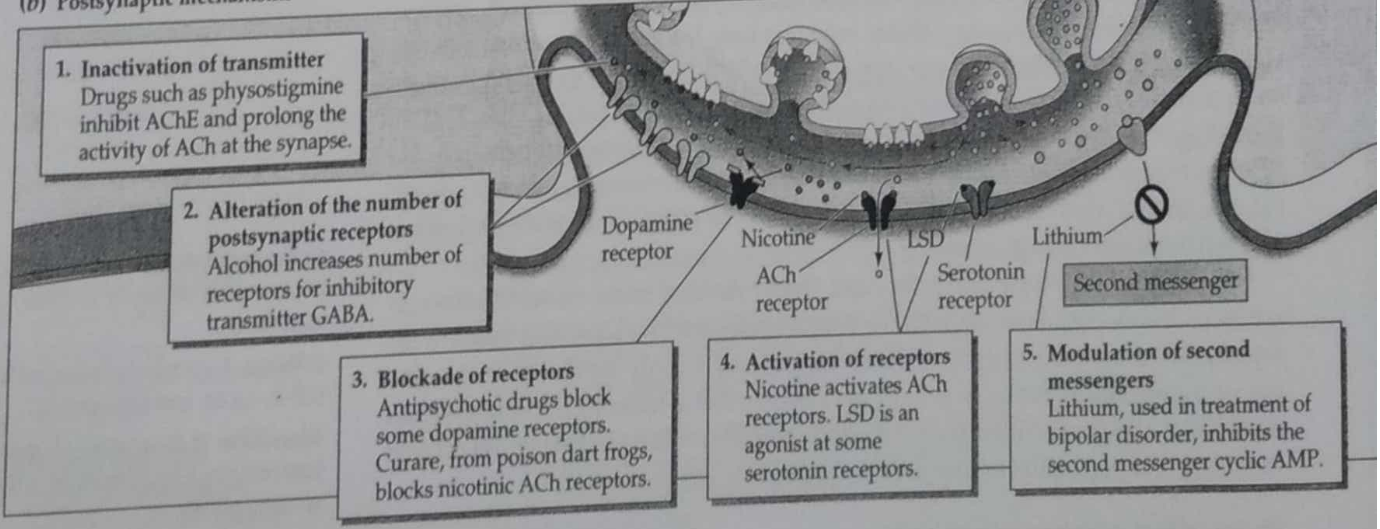
5. **Storage of transmitters into vesicles** Reserpine causes synaptic vesicles to become "leaky," allowing transmitter molecules to escape and/or be exposed to breakdown enzymes.

6. **Modulation of transmitter release by presynaptic receptors** Caffeine competes with adenosine for presynaptic receptors, thus preventing its inhibitory effects.

7. **Inactivation of transmitter reuptake** Cocaine and amphetamine inhibit reuptake mechanisms, thus prolonging synaptic activity. Certain antidepressants inhibit serotonin reuptake.

8. **Blockade of transmitter metabolism** Monamine oxidase inhibitors (MAOIs) inhibit enzymes that normally inactivate transmitters, consquently transmitter remains in the synapse longer and has greater effect.

(*b*) **Postsynaptic mechanisms**



1. **Inactivation of transmitter** Drugs such as physostigmine inhibit AChE and prolong the activity of ACh at the synapse.

2. **Alteration of the number of postsynaptic receptors** Alcohol increases number of receptors for inhibitory transmitter GABA.

3. **Blockade of receptors** Antipsychotic drugs block some dopamine receptors. Curare, from poison dart frogs, blocks nicotinic ACh receptors.

4. **Activation of receptors** Nicotine activates ACh receptors. LSD is an agonist at some serotonin receptors.

5. **Modulation of second messengers** Lithium, used in treatment of bipolar disorder, inhibits the second messenger cyclic AMP.

4.8 Steps in Synaptic Transmission That Are Affected by Drugs

between nerves and skeletal muscles are nicotinic, curare paralyzes all skeletal muscles, including those used in breathing. We discussed several other drugs that affect postsynaptic receptors when we described the different neurotransmitter systems at the start of this chapter. Behavior can be disrupted not only when transmitter–receptor action is blocked, but also when it is prolonged. For instance, agents that inhibit the enzyme acetylcholinesterase (AChE) allow ACh to remain active at the synapse and alter the timing of synaptic transmission. These *cholinesterase inhibitors*, including certain pesticides and chemical weapons, produce prolonged contraction of muscles and resultant paralysis, as well as overactivity of the parasympathetic nervous system. Additional postsynaptic drug effects are illustrated in Figure 4.8*b*.

Drugs That Affect the Brain Can Be Divided into Functional Classes

In addition to categorizing drugs on the basis of their cellular effects, we can classify them according to their specific effects on behavior and therapeutic applications. In the sections that follow, we will briefly review some of the major categories of psychoactive substances.

Antipsychotic drugs relieve the symptoms of schizophrenia

Originally thought to be an antihistamine in the 1950s, chlorpromazine was accidentally discovered to reduce some of the symptoms of schizophrenia. Subsequent intense research activity identified several other **antipsychotic** drugs (known as **neuroleptics**). The neuroleptics revolutionized the treatment of schizophrenia because they greatly reduce many of the symptoms, such as delusions and frank hallucinations, that prevent patients with this condition from living on their own. These first-generation drugs, classified as **typical neuroleptics**, all share one key feature: they act as selective antagonists of dopamine D_2 receptors. One of the best-known typical neuroleptics, haloperidol (Haldol), exhibits a nearly 100-fold selectivity for D_2 over D_1 receptors.

The 1990s saw the advent of second-generation antipsychotics, known as **atypical neuroleptics**, which feature nondopaminergic actions, especially the blockade of certain serotonin receptors. These atypical neuroleptics, such as clozapine, are claimed to reduce additional symptoms (termed *negative* symptoms, such as social withdrawal and blunted emotional responses) that typical neuroleptics generally do not relieve, although this claim has been disputed (Burton, 2006). Unfortunately, despite progress in its treatment, schizophrenia remains a major health problem. We return to the topic of schizophrenia and its treatment in Chapter 16.

Antidepressants relieve chronic mood problems

Disturbances of mood, or affective disorders, are among the most common of all psychiatric complaints. In the span of one year, about 5.8% of men and 9.5% of women will experience a significant episode of depression, which is the most prevalent affective disorder (World Health Organization, 2001).

The first generation of effective **antidepressant** medications, developed in the 1950s, were the **monoamine oxidase inhibitors (MAOIs)**; modern MAOI antidepressants include tranylcypromine (Parnate) and isocarboxazid (Marplan). One of the major activities of MAOs is to break down monoamine neurotransmitters at synapses, thereby reducing transmitter activity (see Figure 4.8*a*). By inhibiting monoamine oxidase, MAOI drugs allow monoamine neurotransmitters to accumulate at synapses, with an associated improvement in mood.

Increasing synaptic monoamine availability appears to be a key activity of all antidepressants. The second generation of antidepressants—the **tricyclics**—combat depression by increasing the synaptic content of norepinephrine and serotonin. Named for their three-ringed molecular structure, tricyclics such as imipramine (Tofranil) block the reuptake of neurotransmitters into presynaptic axon terminals. More recently developed antidepressants, such as fluoxetine (Prozac), sertraline (Zoloft), and citalopram (Celexa),

antipsychotics A class of drugs that alleviate schizophrenia.

neuroleptics A class of antipsychotic drugs, traditionally dopamine receptor blockers.

typical neuroleptics A major class of antischizophrenic drugs that share an antagonist activity at dopamine D_2 receptors.

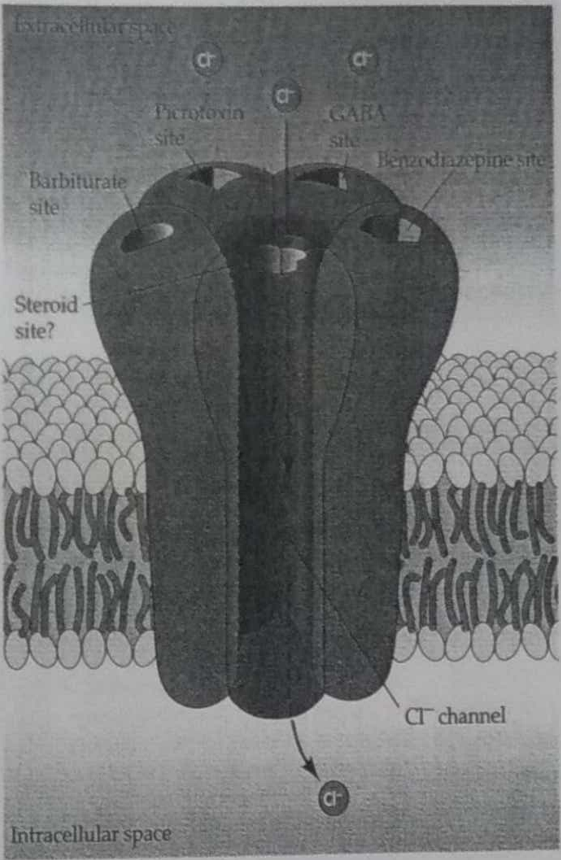
atypical neuroleptics A class of antischizophrenic drugs that have actions other than the dopamine D_2 receptor antagonism that characterizes the typical neuroleptics.

antidepressants A class of drugs that relieve the symptoms of depression.

monoamine oxidase inhibitor (MAOI, or MAO inhibitor) An antidepressant drug that blocks the breakdown of monoamine neurotransmitters by the enzyme monoamine oxidase, resulting in an accumulation of monoamine transmitters in synapses.

tricyclic antidepressants A class of drugs that act by increasing the synaptic accumulation of serotonin and norepinephrine.

are **selective serotonin reuptake inhibitors (SSRIs)**; as the name indicates, these drugs alleviate depression by selectively allowing serotonin to accumulate in synapses. These newer antidepressants lack some of the undesirable side effects of tricyclics, but they can take as long as 6 to 8 weeks to have full effect. We will discuss the causes and treatment of affective disorders in more detail in Chapter 16.



4.9 The GABA$_A$ Receptor Has Many Different Binding Sites The GABA$_A$ complex is made up of five protein subunits that penetrate the cell membrane and surround a Cl⁻ ion channel at the core. These subunits contain many different recognition and receptor sites; some of the most important ones are labeled here. GABA$_A$ receptors are widespread in the brain and are crucial for normal inhibitory processes.

Anxiolytics combat anxiety

Most of us occasionally suffer feelings of vague dissatisfaction or apprehension that we call anxiety, but some people are stricken by disabling emotional distress that resembles abject fear and terror. Severe anxiety that prevents people from carrying on normal daily activities is estimated to afflict about 8% of adult Americans. These clinical states of anxiety include panic attacks, phobias (such as the fear of taking an airplane or even of leaving the house), and generalized anxiety (see Chapter 16).

Humans have long sought relief from anxiety through the ingestion of **anxiolytics** (from the word *anxiety* and the Greek *lytikos*, "able to loosen"). Sometimes also called *tranquilizers*, anxiolytics belong to the general category of **depressants**: drugs that depress or reduce nervous system activity. Alcohol is perhaps the original anxiolytic, but its anxiety-fighting properties come at the cost of intoxication, addiction potential, and neuropsychological impairment with long-term abuse. Opiates and barbiturates have also been used to relieve anxiety, but they have strongly sedative effects, strong addiction potential, and significant risk of accidental overdose.

First discovered in the 1960s, **benzodiazepine agonists** have proven to be safe and effective anxiolytics, and they are among the most heavily prescribed drugs. One of the most familiar members of this class of drug, the benzodiazepine diazepam (trade name Valium), binds to specific sites on GABA$_A$ receptors and enhances the activity of GABA (Walters et al., 2000). Because GABA$_A$ receptors are inhibitory, benzodiazepines help GABA to produce larger inhibitory postsynaptic potentials than would be caused by GABA alone.

As we discussed earlier, GABA$_A$ receptors have several different binding sites—some that facilitate and some that inhibit the effect of GABA (**Figure 4.9**)—so many different drugs can interact with this receptor complex. For example, benzodiazepines bind to a unique modulatory site on the receptor complex that is distant from where GABA itself binds. The benzodiazepine-binding site is thus an **orphan receptor**—a receptor for which an endogenous ligand has not been conclusively identified—and the hunt for its endogenous ligand has been intense. A possible endogenous ligand is **allopregnanolone,** a steroid derived from the hormone progesterone. Allopregnanolone is elevated during stress and has a calming effect. Alcohol ingestion also increases brain concentrations of allopregnanolone (VanDoren et al., 2000), so this steroid may mediate some of the calming influence of alcohol. It is likely that several progesterone-like **neurosteroids** (steroids produced in the brain) act on GABA$_A$ receptors to produce anxiolytic, analgesic, and anticonvulsant effects (Belelli and Lambert, 2005).

New generations of anxiolytics that are under development affect other transmitter systems, notably serotonin. The serotonergic agonist buspirone (Buspar) is an effective anxiolytic that lacks the sedative effects of benzodiazepines. Although it is known to be a 5HT$_{1A}$ agonist and, with lower affinity, a partial agonist of dopamine D$_2$ receptors, the exact mechanism of buspirone's anxiolytic action remains unknown.

Alcohol has several effects

Alcohol has traveled the full route of human history, no doubt because it is so easily produced by the fermentation of fruit or grains, and thus is an ingredient of many types of pleasant beverages. Taken in moderation, alcohol is harmless or even beneficial to the

selective serotonin reuptake inhibitor (SSRI) A drug that blocks the reuptake of transmitter at serotonergic synapses.

anxiolytics A class of substances that are used to combat anxiety.

depressants A class of drugs that act to reduce neural activity.

benzodiazepine agonists A class of antianxiety drugs that bind to sites on GABA$_A$ receptors.

orphan receptor Any receptor for which no endogenous ligand has yet been discovered.

allopregnanolone A naturally occurring steroid that modulates GABA receptor activity in much the same way that benzodiazepine anxiolytics do.

neurosteroids Steroids produced in the brain.

health of adults; for example, consumption of one drink or so per day is associated with reduced risk of cardiovascular and Alzheimer's diseases, and with improved control of blood sugar levels (Davies et al., 2002; Leroi et al., 2002; Mukamal et al., 2003). *Excessive* alcohol consumption, however, is very damaging and linked to more than 60 disease processes.

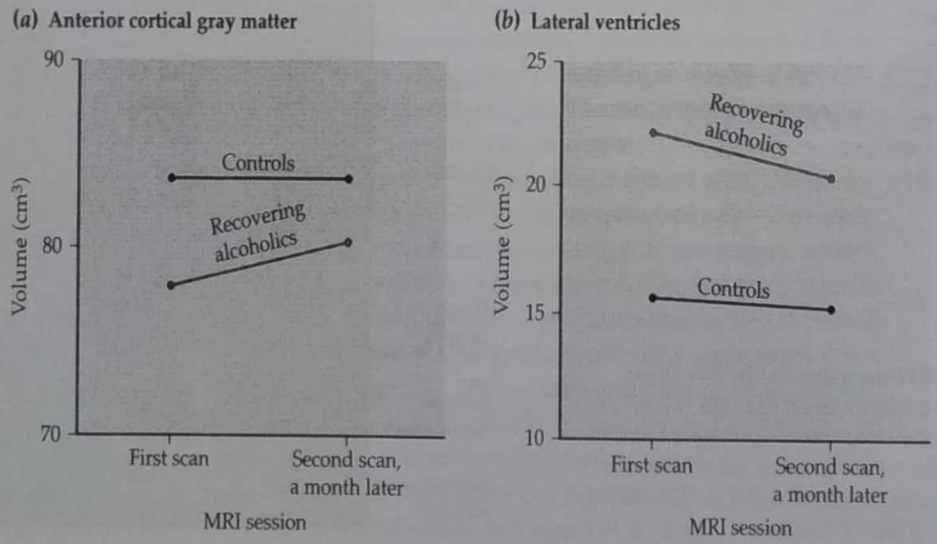
The psychoactive effect of alcohol in the nervous system is biphasic: an initial stimulant phase is followed by a more prolonged depressant phase. GABA plays an important role in mediating the effects of alcohol in the brain. In a similar manner to the benzodiazepines, but acting via a different recognition site, alcohol activates the $GABA_A$ receptor–coupled chloride channel (see Figure 4.9), thereby increasing postsynaptic inhibition by allowing more Cl^- ions to enter neurons. This action contributes to social disinhibition, as well as the impairment of motor coordination that occurs after a few drinks (Hanchar et al., 2005). Alcohol also affects other transmitters. For example, low doses of alcohol stimulate dopamine pathways, and the resulting increase in dopamine may be related to the euphoriant properties of alcohol.

Chronic abuse of alcohol damages nerve cells. Cells of the superior frontal cortex, Purkinje cells of the cerebellum, and hippocampal pyramidal cells show particularly prominent pathological changes. Some of these degenerative effects of chronic alcohol use may be due to a secondary consequence of alcoholism: poor diet. For example, chronic alcoholism is accompanied by severe thiamine deficiency, which can lead to neural degeneration and Korsakoff's syndrome (see Chapter 17). And alcohol abuse by expectant mothers can cause grievous permanent brain damage to the developing fetus (termed **fetal alcohol syndrome**), a topic to which we will return in Chapter 7 (see Figure 7.24). In fact, it is not clear whether it is safe for pregnant women to consume *any* alcohol, even small quantities; a few studies have suggested subtle changes in cognitive function of babies exposed to only moderate levels of alcohol in utero (Day et al., 2002; Huizink and Mulder, 2006).

Kril et al. (1997) reported that the frontal lobes of people suffering from alcoholism—especially the superior frontal association cortex—are the brain areas that are most affected by chronic alcohol use. However, some of the anatomical changes associated with chronic alcoholism may be reversible with abstinence. In rats, chronic exposure to alcohol reduces the number of synapses on neurons in some regions, but this number returns to normal levels after alcohol treatments stop (Dlugos and Pentney, 1997). Similarly, in humans suffering from alcoholism, MRI studies show an increase in the volume of cortical gray matter and associated reduction in ventricular volume within weeks of giving up alcohol (**Figure 4.10**) (Pfefferbaum et al., 1995).

There is a strong hereditary component to alcoholism, as indicated by human studies and selective breeding experiments in rats. In humans, 20% to 50% of the sons of

fetal alcohol syndrome (FAS) A disorder, including mental retardation and characteristic facial anomalies, that affects children exposed to too much alcohol (through maternal ingestion) during fetal development.



4.10 The Effects of Alcohol on the Brain MRI studies of humans who suffer from alcoholism show that abstaining from alcohol for 30 days increases the volume of cortical gray matter (a) and decreases the volume of the lateral ventricles (*b*). (After Pfefferbaum et al., 1995.)

4.11 The Source of Opium and Morphine The opium poppy has a distinctive flower and seedpod. The bitter flavor and CNS actions of opium may provide the poppy plant a defense against being eaten.

people who suffer from alcoholism and 3% to 8% of the daughters eventually suffer from alcoholism themselves. Rates of alcoholism in the first-degree relatives of people who suffer from alcoholism are several times higher than are rates for the general population (Schuckit and Smith, 1997). The combination of genetic vulnerability and a stressful environment probably explains many cases of alcoholism (McGue, 1999).

Even in the absence of clear-cut alcoholism, periodic overconsumption of alcohol—*bingeing*—may cause brain damage. Fulton Crews and coworkers have reported that, in as little as 4 days, rats bingeing on alcohol exhibit neural degeneration in several areas of the brain. Damage is especially evident in the olfactory bulbs and in limbic structures connected with the hippocampus, and it is associated with impairments of cognitive ability (Obernier et al., 2002). Alcohol bingeing also significantly reduces the rate of neurogenesis—the formation of new neurons—in the adult hippocampus (Nixon and Crews, 2002).

Opiates help relieve pain

Opium, extracted from poppy flower seedpods (**Figure 4.11**), has been used by humans since at least the Stone Age. **Morphine**, the major active substance in opium, is a very effective **analgesic** (painkiller) that has brought relief from severe pain to many millions of people. Unfortunately, morphine also has a strong potential for addiction, as does its close relative **heroin** (diacetylmorphine).

Opiate drugs such as morphine bind to specific receptors—**opioid receptors**—that are concentrated in certain regions of the brain. Opioid receptors are found in the limbic and hypothalamic areas of the brain, and they are particularly rich in the locus coeruleus and in the gray matter that surrounds the aqueduct in the brainstem (known as the **periaqueductal gray**) (**Figure 4.12**). Injection of morphine directly into the periaqueductal gray produces strong analgesia, indicating that this is a region where morphine acts to reduce pain perception (see Chapter 8). The discovery of orphan receptors for opiates came as a surprise and, because the presence of these receptors implied that there must be an endogenous ligand produced within the body, it prompted an intense scientific effort to identify **endogenous opioids**.

opium A heterogeneous extract of the seedpod juice of the opium poppy, *Papaver somniferum*.

morphine An opiate compound derived from the poppy flower.

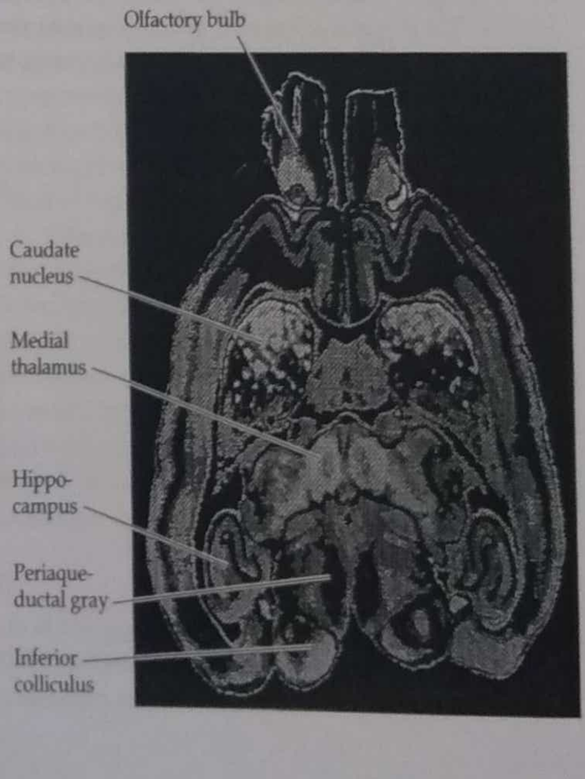
analgesic Referring to painkilling properties.

heroin Diacetylmorphine; an artificially modified, very potent form of morphine.

opioid receptor A receptor that responds to endogenous and/or exogenous opiates.

periaqueductal gray The neuronal body–rich region of the midbrain surrounding the cerebral aqueduct that connects the third and fourth ventricles.

endogenous opioids A family of peptide transmitters that have been called the body's own narcotics. The three kinds are enkephalins, endorphins, and dynorphins.



4.12 The Distribution of Opioid Receptors in the Rat Brain This horizontal section (rostral is at the top) shows opioid receptors widely distributed in the brain (the areas of highest binding are shown in yellow, orange, and red). They are concentrated in the medial thalamus and in some brainstem areas: the periaqueductal gray and the inferior colliculus. (Courtesy of Miles Herkenham, National Institute of Mental Health.)

4.13 An Indoor Marijuana Farm Although growing the marijuana plant (*Cannabis sativa*) is widely prohibited, it is believed to be the largest cash crop in several U.S. states, parts of Canada, and other locations around the globe. Growers have developed sophisticated hydroponic techniques for growing highly potent strains of cannabis in indoor "grow ops."

A pair of endogenous peptides that bind to opioid receptors were eventually identified and named **enkephalins** (from the Greek *en*, "in," and *kephale*, "head") (Hughes et al., 1975). Research with animal subjects demonstrated that, like morphine, enkephalins relieve pain and are addictive. Only a small part of the enkephalin molecule is the same as the morphine molecule, but this common part is what binds to the opioid receptor. Further research uncovered additional families of endogenous opiates: the **endorphins** (a contraction of *endogenous morphine*) and the **dynorphins** (short for *dynamic endorphins*, in recognition of their potency and speed of action.)

There are three main kinds of opioid receptors—the δ, κ, and μ opioid receptors—differing in their affinity for various *opiatergic* drugs (C. J. Evans et al., 1992; J. B. Wang et al., 1993; Yasuda et al., 1993). All three opioid receptor subtypes are G protein–coupled metabotropic receptors.

Cannabinoids have a wide array of effects

Marijuana and related preparations, such as hashish, are obtained from the *Cannabis sativa* plant (**Figure 4.13**) and are the most widely used of all illicit drugs. Typically ingested via smoking, marijuana contains dozens of active ingredients, chief among which is the compound **Δ9-tetrahydrocannabinol (THC)** (Gaoni and Mechoulam, 1964). The subjective experience of marijuana use is quite variable among individuals: relaxation and mood alteration are the most frequent effects; but stimulation, hallucination, and paranoia also occur in some cases. Sustained use of marijuana can cause addiction (Maldonado and Rodríguez de Fonseca, 2002), and frequent smoking of marijuana, like tobacco, can contribute to respiratory diseases. There is also some evidence to suggest that significant use by adolescents increases the risk of psychiatric disturbances in adulthood (Henquet et al., 2005).

As was the case with opiates and benzodiazepines, researchers found that the brain contains orphan cannabinoid receptors that mediate the effects of compounds like THC. Cannabinoid receptors are concentrated in the substantia nigra, the hippocampus, the cerebellar cortex, and the cerebral cortex (**Figure 4.14**) (Devane et al., 1988); other regions, such as the brainstem, show few of these receptors. There are at least two subtypes of cannabinoid receptors—CB$_1$ and CB$_2$ (Gerard et al., 1991; Pertwee, 1997)—both of which are G protein–coupled metabotropic receptors. Genetic disruption of CB$_1$ receptors is sufficient to make mice unresponsive to the rewarding properties of cannabinoid drugs (Ledent et al., 1999). Only the CB$_1$ receptor is found in the nervous system; CB$_2$ receptors are especially prominent in the immune system.

The discovery of cannabinoid receptors touched off an intensive search for an endogenous ligand, and several such compounds—termed **endocannabinoids**—were identified. Interestingly, endocannabinoids can function as retrograde messengers, conveying messages from the postsynaptic cell to the presynaptic cell. This retrograde signal is thought to modulate the release of neurotransmitter by the presynaptic nerve terminal (R. I. Wilson and Nicoll, 2002). The most studied endocannabinoid is **anandamide** (from the Sanskrit *ananda*, "bliss") (Devane et al., 1992), which has diverse functional effects, including alterations of memory formation, appetite stimulation, reduced sensitivity to pain, and protection from excitotoxic brain damage (Marsicano et al., 2003; P. B. Smith et al., 1994). Other endocannabinoids under active investigation include 2-arachidonylglycerol (2-AG) (Stella et al., 1997) and oleamide (Leggett et al., 2004).

enkephalins One of three kinds of endogenous opiates.

endorphins One of three kinds of endogenous opiates.

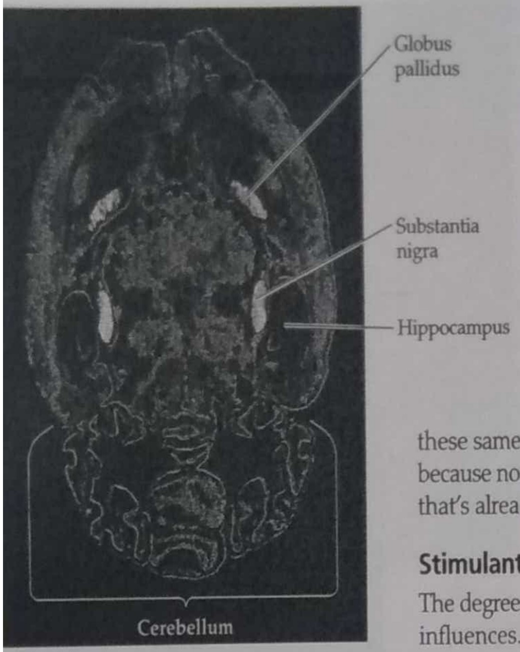
dynorphins One of three kinds of endogenous opiates.

marijuana A dried preparation of the *Cannabis sativa* plant, usually smoked to obtain THC.

Δ9-tetrahydrocannabinol (THC) The major active ingredient in marijuana.

endocannabinoid An endogenous ligand of cannabinoid receptors; thus, an analog of marijuana that is produced by the brain.

anandamide An endogenous substance that binds the cannabinoid receptor molecule.



4.14 The Distribution of Cannabinoid Receptors in the Rat Brain The areas of highest binding are indicated by yellow, orange, and red in this horizontal section. (Courtesy of Miles Herkenham, National Institute of Mental Health.)

The study of endocannabinoids will aid the search for drugs that share the beneficial effects of marijuana: relieving pain, lowering blood pressure, combating nausea, lowering eye pressure in glaucoma, and so on. The documented use of cannabis for medicinal purposes spans some 5000 years, but treatment with "medical marijuana" remains illegal in most jurisdictions. It is ironic that synthetic cannabinoids patented by drug companies could eventually be legally prescribed to patients with these same medical conditions. In a sense, marijuana use is not legalized in these cases because no Wall Street company stands to profit from it. You can't file a patent for a plant that's already been in use for millennia.

Stimulants increase the activity of the nervous system

The degree of activity of the nervous system reflects a balance of excitatory and inhibitory influences. Stimulants are drugs that tip the balance toward the excitatory side; they therefore have an alerting, activating effect. Many naturally occurring and artificial stimulants are widely used; examples include amphetamine, nicotine, caffeine, and cocaine. Some stimulants act directly by increasing excitatory synaptic potentials. Others act by blocking normal inhibitory processes; one example we've seen already is the blocking of adenosine by caffeine. Paradoxically, stimulants such as methylphenidate (Ritalin) have a calming effect in humans with attention deficit hyperactivity disorder (ADHD); this activity may be mediated by changes in serotonergic activity (Gainetdinov et al., 1999).

NICOTINE Tobacco is native to the Americas, where European explorers first encountered smoking; these explorers brought tobacco back to Europe with them. Tobacco use subsequently became much more widespread, especially following technological innovations that made tobacco easier to smoke, in the form of cigarettes (W. Bennett, 1983). Exposed to the large surface of the lungs, the **nicotine** from cigarettes enters the blood and brain much more rapidly than does nicotine from snuff, chewing tobacco, or smoke that is not deeply inhaled, such as pipe and cigar smoke. When nicotine enters the bloodstream, it increases the heart rate, blood pressure, secretion of hydrochloric acid in the stomach, and motor activity of the bowel. These neural effects, quite apart from the effects of tobacco tar on the lungs, contribute to the unhealthful consequences of heavy and prolonged use of tobacco products. However, nicotine has also long been known to enhance aspects of cognitive performance.

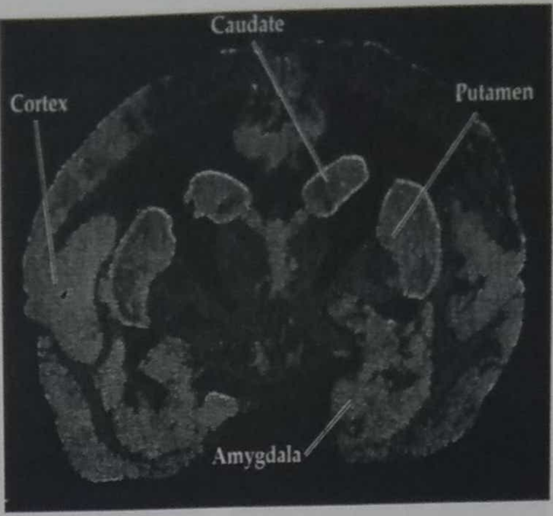
Nicotine activates one class of ACh receptors, which, as we learned earlier, are called nicotinic receptors. Most nicotinic receptors are found at neuromuscular junctions and in neurons of the autonomic ganglia, but many are also present in the central nervous system and likewise are directly stimulated by nicotine. Using a sophisticated genetic model in which certain nicotinic ACh receptors are expressed only in discrete brain regions, researchers have shown that nicotine acts on the ventral tegmental area to exert both its rewarding/addicting effects and improvements in cognitive performance (Maskos et al., 2005). (We will discuss the VTA in more detail when we discuss positive reward models later in the chapter.)

COCAINE For hundreds of years, people in Bolivia, Colombia, and Peru have been using the leaves of the *coca shrub*—either chewed or brewed as a tea—to increase endurance, alleviate hunger, and promote a sense of well-being. This use of coca leaves does not seem to cause problems. The artificially purified coca extract (**cocaine**), however, is a powerfully addictive alkaloid stimulant that has harmed millions of lives.

nicotine A compound found in plants, including tobacco, that acts as an agonist on a large class of cholinergic receptors.

cocaine A drug of abuse, derived from the coca plant, that acts by potentiating catecholamine stimulation.

First isolated in 1859, cocaine was added to beverages (such as *Coca-Cola*) and tonics for its stimulant qualities, and subsequently it was used s a local anesthetic (it is in the same chemical family as procaine, trade ame Novocain) and an antidepressant. In addition, it was widely used s a psychostimulant until 1932, when it gave way to amphetamine, which acts much like cocaine but was easier to obtain (amphetamine was sold in inhalers for nasal congestion, and some people cracked open nhalers to get the drug). When legal restrictions on amphetamine raised its price in the 1960s, cocaine use rose again. Many users snort cocaine powder, which rapidly enters the bloodstream via the nasal route (see Table 4.2).



4.15 Cocaine-Binding Sites in the Monkey Brain This autoradiograph of a coronal section shows the distribution of cocaine-binding sites. The areas of the highest binding are shown by orange and yellow. (Courtesy of Bertha K. Madras.)

Crack is a smokable form of cocaine that appeared in the mid-1980s. Because cocaine in this form enters the blood and the brain more rapidly, crack cocaine is even more addictive than cocaine powder. Like other psychostimulants, cocaine acts by blocking monoamine transporters, especially those for dopamine (**Figure 4.15**), slowing reuptake of the transmitters and therefore boosting their effects. Cocaine may have neurotoxic effects, and an overdose can provoke marked changes in cerebral blood flow, including strokes (Holman et al., 1993), as well as reduction in cortical gray matter density (Franklin et al., 2002). As a consequence of sensitization, which we discussed earlier, chronic cocaine use can provoke symptoms similar to psychosis. Cessation of cocaine use often produces very uncomfortable withdrawal symptoms: initial agitation and powerful drug cravings, followed by depression and an inability to enjoy anything else in life. Decreases in cerebral glucose metabolism are evident for several months after cocaine use is discontinued. People who use cocaine along with other substances run the additional risk of **dual dependence**, in which the interaction of two (or more) drugs produces an additional addictive state. For example, cocaine metabolized in the presence of ethanol (alcohol) yields an active metabolite called *cocaethylene*, to which the user may develop a further addiction (D. S. Harris et al., 2003).

Some children are initially exposed to cocaine while in the womb, and there has been widespread fear that exposure during fetal life might produce irreversible harm to the development of brain and behavior (Vogel, 1997). One cocaine-related developmental effect on infants is a decreased ability to focus attention—an effect that is also seen in rats exposed to prenatal cocaine (Garavan et al., 2000).

AMPHETAMINE The molecular structure of the synthetic psychostimulant **amphetamine** closely resembles that of the catecholamine transmitters (norepinephrine, epinephrine, and dopamine). Amphetamine and the even more potent methamphetamine (*speed*) cause the release of these transmitters from presynaptic terminals even in the absence of action potentials, and when action potentials *do* reach the axon terminals, amphetamine also potentiates the subsequent release of transmitter. Furthermore, once transmitter has been released, amphetamine enhances activity in two ways: (1) by blocking the reuptake of catecholamines into the presynaptic terminal, and (2) by providing an alternative target for the enzyme (monoamine oxidase) that normally inactivates them.

Because amphetamine stimulates and enhances the activity of the catecholamine transmitters, it has a variety of behavioral effects. On a short-term basis, it produces heightened alertness and even euphoria, and it promotes sustained effort without rest or sleep and with lowered fatigue. However, although a person may be able to accomplish more work and feel more confident by using amphetamine, most studies show that the quality of work is not improved by the drug—that is, that the drug increases motivation but not cognitive ability.

Tolerance to the effects of amphetamine develops rapidly, so chronic users have to take larger and larger doses, leading to sleeplessness, severe weight loss, and general deterioration of mental and physical condition. Prolonged use of amphetamine may lead to symptoms that closely resemble those of paranoid schizophrenia: compulsive, agi-

dual dependence Dependence for emergent drug effects that occur only when two drugs are taken simultaneously.

amphetamine A molecule that resembles the structure of the catecholamine transmitters and enhances their activity.

cocaine- and amphetamine-regulated transcript (CART) A peptide produced in the brain when an animal is injected with either cocaine or amphetamine. Associated with the appetite control circuitry of the hypothalamus.

hallucinogens A class of drugs that alter sensory perception and produce peculiar experiences.

LSD Also called *acid*. Lysergic acid diethylamide, a hallucinogenic drug.

phencyclidine (PCP) Also called *angel dust*. An anesthetic agent that is also a psychedelic drug.

dissociative drug A type of drug that produces a dreamlike state in which consciousness is partly separated from sensory inputs.

tated behavior and irrational suspiciousness. In fact, some amphetamine users have been misdiagnosed as having schizophrenia (see Chapter 16). Amphetamine acts on the autonomic nervous system to produce high blood pressure, tremor, dizziness, sweating, rapid breathing, and nausea. Worst of all, people who chronically abuse speed display symptoms of brain damage long after they quit using the drug (Ernst et al., 2000).

Cocaine or amphetamine treatments induce the brain to produce a peptide called, naturally enough, **cocaine- and amphetamine-regulated transcript (CART)**. Injections of CART in a particular brain region (the ventral tegmental area, which we'll discuss a little later in the chapter) is very rewarding for rats (Kimmel et al., 2000), suggesting that CART is involved in the pleasurable aspects of these drugs. The CART system also helps regulate appetite (see Chapter 13).

Hallucinogenic and dissociative drugs alter sensory perception

Drugs classified as **hallucinogens** alter sensory perceptions in dramatic ways and produce peculiar experiences. But the term *hallucinogen* is a misnomer because, whereas a hallucination is a novel perception that takes place in the absence of sensory stimulation (hearing voices, or seeing something that isn't there), the drugs in this category tend to alter or distort existing perceptions. The effects of lysergic acid diethylamide (**LSD**, or *acid*) and related substances like mescaline (*peyote*) and psilocybin (*magic mushrooms*), are predominantly visual. Users often see fantastic images with intense colors, and they are often aware that these strangely altered perceptions are not real events.

Hallucinogenic agents are diverse in their neural actions. For example, mescaline, the drug extracted from the peyote plant, affects noradrenergic and serotonergic systems. Many hallucinogens, including LSD, mescaline, psilocybin, and others, tend to act as serotonin receptor agonists or partial agonists, especially at $5HT_{2A}$ receptors. Other hallucinogens, such as muscarine, found in some mushrooms, affect the ACh system.

You may have guessed that Albert Hofmann (**Figure 4.16**), whose story opened this chapter, was the discoverer of LSD. In fact, the study of LSD's activities became the focus of his professional career, summarized in his 1981 book, *LSD: My Problem Child*. Following its discovery, LSD was intensively studied as a possible psychiatric treatment. Starting in the 1950s, many investigators worked on LSD, hoping it would provide a useful model of psychosis that would suggest clues about the biochemical processes in mental illnesses.

4.16 The Father of LSD Albert Hofmann discovered LSD in 1943 and devoted the remainder of his career to studying it. A prohibited drug in most jurisdictions, LSD is distributed on colorful blotter paper. This example, picturing Hofmann and the LSD molecule, is made up of 1036 individual doses (or "hits").

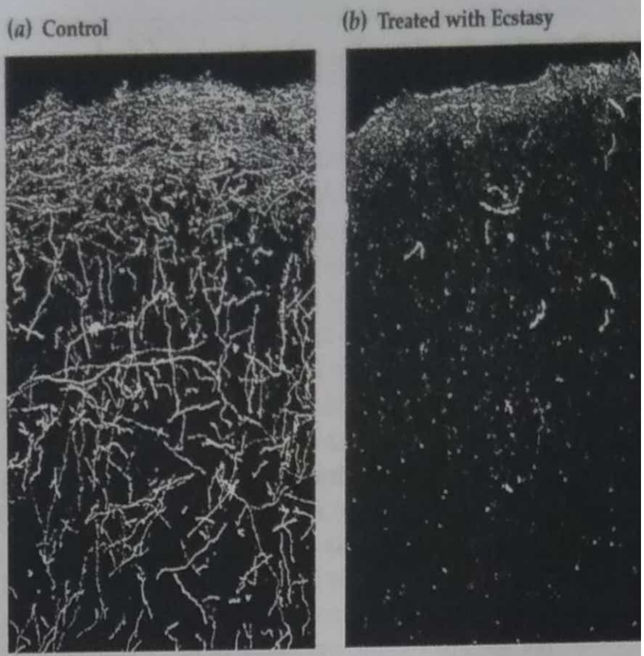
The structure of LSD resembles that of serotonin, and LSD was soon found to act on serotonin receptors, probably evoking visual phenomena by activating serotonin receptors of the visual cortex. Former users of LSD sometimes report experiencing flashbacks—that is, experiences as if they had taken a dose of drug, even though they are drug-free. These episodes can follow even brief use of LSD, but it is not yet clear whether they reflect permanent neural changes or a special form of memory.

Phencyclidine (commonly known as **PCP** or *angel dust*) was developed in 1956 as a potent analgesic and anesthetic agent. Classified as a **dissociative drug** because it produces feelings of depersonalization and detachment from reality, it was soon dropped from use in anesthesia because patients reported effects such as agitation, excitement, delirium, hostility, and disorganization of perceptions. PCP continues to be used as a street drug, principally because of its hallucinogenic actions. Even at relatively low doses, PCP produces numerous undesirable effects, including combativeness and catatonia (stupor and immobility). Higher doses or repeated use can lead to long-lasting profound confusion, or convulsions and coma. The similarity between PCP's effects and psychosis has led some researchers to propose PCP as a chemical model of schizophrenia (see Chapter 16). In animal models, PCP causes degeneration in the hippocampus and the cingulate gyrus.

PCP antagonizes the NMDA receptor (see Figure 16.10), perhaps at a special binding site, and it stimulates release of the transmitter dopamine (Gorelick and Balster, 1995). PCP's molecular relative, **ketamine** (nicknamed *Special K*), is a less potent NMDA antagonist that is used as a dissociative anesthetic agent. PET studies of the effects of ketamine on the brains of healthy volunteers showed focal increases of metabolic activity in the prefrontal cortex (Breier, Malhotra, et al., 1997), so perhaps PCP also acts there. Like PCP, ketamine in high doses produces transient psychotic symptoms in volunteers.

Ecstasy is the street name for the hallucinogenic amphetamine derivative **MDMA** (3,4-methylenedioxymethamphetamine). Major actions of MDMA in the brain include an increase in the release of serotonin, stimulation of $5HT_{2A}$ receptors, and changes in the levels of dopamine and certain hormones, such as prolactin. Exactly how these activities account for the subjective effects of MDMA—positive emotions, empathy, euphoria, a sense of well-being, and colorful visual phenomena—remains to be established.

In lab animals, chronic use of Ecstasy produces persistent effects on serotonin-producing neurons, such as a prolonged reduction in serotonin metabolites. In addition, fine serotonergic axons and axon terminals are at least temporarily damaged, probably by metabolites of MDMA (T. J. Monks et al., 2004), although its not clear if the cell bodies of serotonergic cells also suffer longer-lasting damage. **Figure 4.17** shows a marked reduction in serotonin axons in the cortex and hippocampus of a squirrel monkey treated with MDMA 18 months earlier (C. Fischer et al., 1995). Humans who take MDMA also display reduced serotonin binding in the cortex (Semple et al., 1999). These changes may be related to psychiatric and cognitive effects, including memory disturbances, reported after MDMA use (Wareing et al., 2000). MDMA use may also result in depression (Sumnall and Cole, 2005).


(a) Control

(b) Treated with Ecstasy

4.17 Long-Term Effects of a Single Dose of Ecstasy on the Monkey Brain Serotonin axons in the dorsal cortex of *(a)* a control squirrel monkey and *(b)* a squirrel monkey treated with a single dose of MDMA (Ecstasy) 18 months earlier. (Fischer et al., 1995; photo courtesy of George Ricaurte.)

Drug Abuse Is Pervasive

Substance abuse and addiction have become a social problem that afflicts many millions of people and disrupts the lives of their families, friends, and associates. Just one example reveals the extent of the problem: in the United States each year, more men and women die of smoking-related lung cancer than of colon, breast, and prostate cancers *combined*. In addition to the personal impact of so much illness and early death, there are dire social costs: huge expenses for medical and social services; millions of hours lost in the workplace; elevated rates of crime associated with illicit drugs; and scores of children who are damaged by their parents' substance abuse behavior, in the uterine environment as well as in the childhood home. In the discussion that follows, we will examine the mechanisms of drug abuse, the different approaches to understanding drug abuse, how individuals vary in their vulnerability to drug abuse, and how drug abuse can be prevented and treated.

The mechanisms of drug abuse have been studied extensively

The self-administration of intoxicating substances is a behavior that we may share with a variety of wild animals (R. K. Siegel, 1989). Although the claim that wild elephants get drunk by eating fermented fruit is almost certainly a myth, it is nevertheless true that elephants like drinking alcohol (S. Morris et al., 2006). Furthermore, when elephants on game preserves are stressed by a reduction in their ability to range, they self-medicate by increasing their intake of alcohol. Similarly, intoxicating mushrooms are eaten by cattle, reindeer, and rabbits. And as we will see, in the lab it is relatively easy to get experimental animals to dose themselves with intoxicating substances.

Researchers have proposed numerous models of substance abuse and addiction varying in their emphasis on physiological, behavioral and environmental factors (M. Glantz

ketamine A dissociative anesthetic drug that acts as an NMDA receptor antagonist.

MDMA Also called *Ecstasy*. A drug of abuse, 3,4-methylenedioxymethamphetamine.

OX 4.2 The Terminology of Substance-Related Disorders

For definitions of mental disorders, psychiatrists, psychologists, and neuroscientists rely on the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revised), known as the *DSM IV-TR* (American Psychiatric Association, 2000). The *DSM IV-TR* provides descriptions of a spectrum of substance-related disorders. Within this category, **dependence** (commonly called *addiction*) is a more severe disorder than **substance abuse**.

The essential feature of dependence on psychoactive substances (e.g., alcohol, tobacco, cocaine, marijuana) is "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems." To be diagnosed as dependent, a person must meet at least three of seven criteria relating to patterns of consumption, craving, expenditure of time and energy in serving the addiction, and impact on the other aspects of the person's life. Furthermore, once dependence has been diagnosed, it is placed on a scale ranging from mild to moderate to severe, depending on how many of the seven criteria have been met.

When the minimum criteria for dependence have not been met but there is evidence of maladaptive patterns of substance use that have persisted at least a month or have occurred repeatedly, the diagnosis is substance abuse. The following situations are examples in which a diagnosis of substance abuse is appropriate.

1. A student has substance-related absences, suspensions, or expulsion from school.
2. A person is repeatedly intoxicated with alcohol in situations that are hazardous—for example, when driving a car, operating machinery, or engaging in risky recreational activities such as swimming or rock climbing.
3. A person has recurrent substance-related legal problems—for example, arrests for disorderly conduct, assault and battery, or driving under the influence.

dependence Also called *addiction*. The strong desire to self-administer a drug of abuse.

substance abuse A maladaptive pattern of substance use that has lasted more than a month but does not fully meet the criteria for dependence.

and Pickens, 1992). We will focus primarily on addiction to cocaine, the opiate drugs (such as morphine and heroin), nicotine, and alcohol because these substances have been studied the most thoroughly. According to the 2005 National Survey of Drug Use and Health, some 22.2 million people in the United States alone suffer from substance-related disorders (Substance Abuse and Mental Health Services Administration, 2006). Worldwide, the number is probably in the hundreds of millions. Some terminology specific to substance dependence (addiction) and substance abuse is clarified in **Box 4.2**.

Because addictive substances are no exception to the general rule that drugs produce multiple effects, it is difficult to determine which mechanisms are most important in producing dependence. For example, we have already noted that cocaine has the following major characteristics: (1) it is a local anesthetic; (2) it produces intensely pleasurable feelings, so it is a rewarding agent; and (3) it is a psychomotor stimulant. The opiate drugs, like morphine and heroin, also produce intensely rewarding sensations, but they are depressants, not stimulants. Like cocaine, the opiates produce a strong physical dependence and powerful withdrawal symptoms on cessation of use. But opiates tend to produce only tolerance, whereas at least some of the actions of cocaine induce sensitization. So a comprehensive theory of drug abuse and addiction must be able to account for dependence across a wide variety of compounds with very different effects.

Several perspectives help us understand drug abuse

Any comprehensive model of drug abuse has to answer several difficult questions: What social and environmental factors in a person's life cause her to start abusing a substance? What factors cause her to continue? What are the physiological mechanisms that make a substance rewarding? What is addiction, physiologically and behaviorally, and why is it so hard to quit? The major models that we sketch here each address some but not all of these issues; an integrative approach that addresses the entire problem of substance abuse is an urgent but elusive goal.

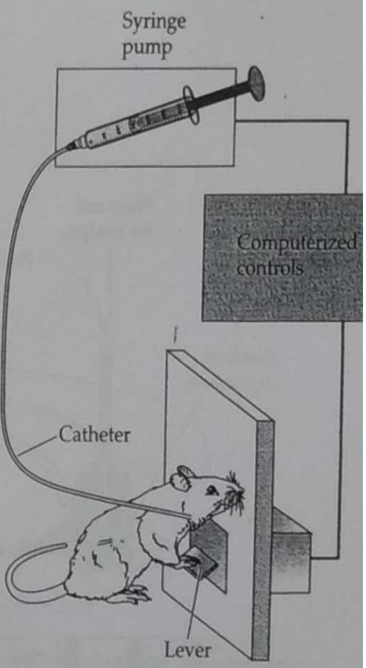
THE MORAL MODEL The earliest approach to explaining drug abuse was to simply blame the substance abuser for a lack of moral character or a lack of self-control. Explanations of this sort often have a religious character and hold that only divine help will free a person from addiction. Applications based on the moral model can be effective. For example, the temperance movement in the United States, beginning around the 1830s, is estimated to have cut per capita consumption of alcohol to about one-third its level in the period from 1800 to 1820 (Rorabaugh, 1976). However, the "Just Say No" campaign championed by former U.S. First Lady Nancy Reagan in the 1980s did not appear to produce significant reductions in drug abuse.

THE DISEASE MODEL In this view, the person who abuses drugs requires medical treatment rather than moral exhortation or punishment. This view also justifies spending money to research drug abuse in the same way that money is spent to research other diseases. It is still not clear, however, exactly what kind of a disease addiction is, and the model is mute regarding the process by which the addiction starts.

Usually the term *disease* is reserved for a state in which we can identify an abnormal physical or biochemical condition. Investigators have not been able to find such an abnormal physical or biochemical condition in the case of drug addiction, other than the immediate effects of the drug itself (although mounting evidence suggests that some people are genetically more susceptible to addiction than others). Nevertheless, this model continues to appeal to many, and an intensive effort is under way to identify the physiological "switch" that establishes addiction from initial exposure.

THE PHYSICAL DEPENDENCE MODEL The physical dependence model, sometimes called the *withdrawal avoidance model*, is based on the unpleasant withdrawal symptoms that occur when a person stops taking a drug that he or she has used frequently. The specific withdrawal symptoms depend on the drug, but they are often the opposite of the effects produced by the drug itself. For example, the withdrawal symptoms of morphine include irritability, tremor, and elevated heart rate and blood pressure. Waves of goose bumps occur, and the skin resembles that of a plucked turkey, which is why abrupt withdrawal without any treatment is called *cold turkey*. Whereas most drugs of abuse produce pleasurable feelings, withdrawal usually induces the opposite: dysphoria. Withdrawal symptoms can be suppressed quickly (within 15 to 20 minutes in the case of morphine) by administration of the withdrawn drug, or a related compound (e.g., heroin withdrawal symptoms can be attenuated by its chemical cousin methadone). This model provides one explanation of why addicts work compulsively to get drugs: to avoid or overcome withdrawal effects.

Because withdrawal symptoms are so striking, some investigators have proposed that development of dependence is the basic characteristic of addiction. But it is clear that people can become dependent on drugs even in the absence of clear physical withdrawal symptoms (Wise, 1996). Are these people *psychologically* addicted rather than *physically* addicted? So far, such a distinction seems irrelevant because either form of addiction can have disastrous, even fatal, consequences. Indeed, the entire theme of this book is that *psychological* processes all have a physical basis in the brain, which is just as real as the muscular contractions that produce shivering or nausea. Clearly a better explanation is needed.



4.18 Experimental Setup for Self-Administration of a Drug by an Animal Here a computer is programmed to administer a small dose of the drug under study after a certain number of lever presses. The number of lever presses that the animal will perform to receive a drug is considered to be a measure of the rewarding properties and addictive potential of that drug; lab animals will press the lever many thousands of times to receive a single small dose of highly addictive compounds like cocaine and methamphetamine.

THE POSITIVE REWARD MODEL The positive reward model of addictive behavior arose from animal research that was started in the 1950s (McKim, 1991). Before that time, researchers believed that animals could not become addicted to drugs, thinking (incorrectly) that animals were not capable of learning an association between the time a drug is injected and the onset of its effects. The subsequent development of a drug self-administration apparatus (**Figure 4.18**) made it possible to quantify the motivation of animals to consume drugs.

From the outset, it was clear that morphine-dependent rats or monkeys would quickly learn to repeatedly press a lever in order to receive a small morphine injection

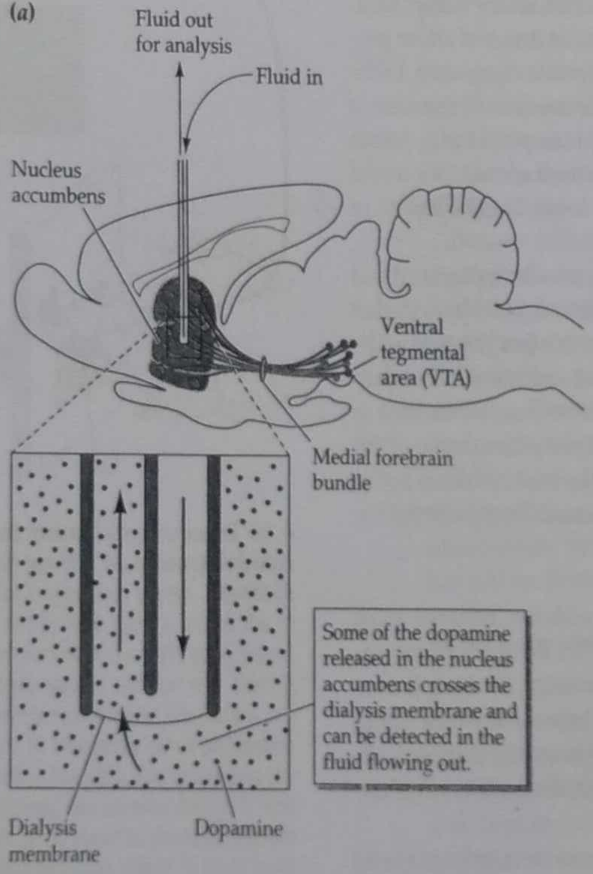
nucleus accumbens A region of the forebrain that receives dopaminergic innervation from the ventral tegmental area.

(T. Thompson and Schuster, 1964). The drug infusion therefore acted like any other experimental reward, such as food or water. Furthermore, even animals that are not already morphine-dependent learn to press a lever for morphine, and they will happily self-administer doses of morphine that are so low that no physical dependence ever develops (Schuster, 1970). Animals will also furiously press a lever to self-administer cocaine and other stimulants that do not produce withdrawal symptoms as marked as the opiates (Koob, 1995; Pickens and Thompson, 1968; Tanda et al., 2000). In fact, cocaine supports some of the highest rates of lever pressing ever recorded.

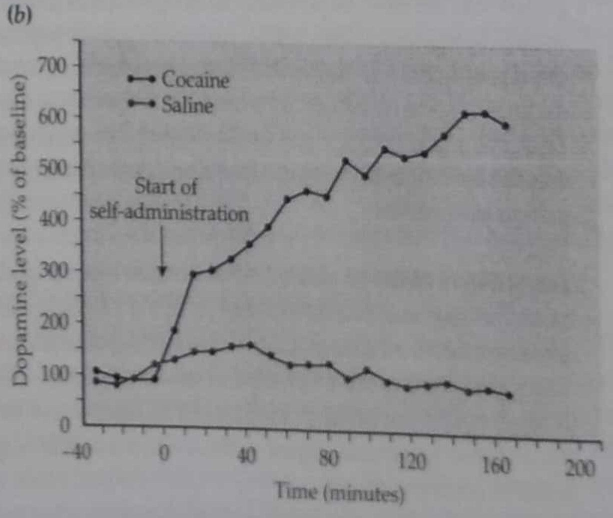
These and other studies contradict the assumptions of both the disease model and the physical dependence model of drug addiction. Although physical dependence may be an important factor in the consumption of some drugs, it is not necessary for self-administration and cannot serve as the sole explanation for drug addiction. Furthermore, these studies indicate that drug self-administration can be interpreted as a behavior controlled by positive rewards (operant conditioning theory; see Box 17.1), without the need to implicate a disease process.

Many addictive drugs cause the release of dopamine in the **nucleus accumbens**, just like more-conventional reinforcers, such as food or sex (Di Chiara et al., 1999); interestingly, dopamine release is also linked to pathological gambling (Reuter et al., 2005). As we mentioned previously, dopamine released from axons originating from the ventral tegmental area (**Figure 4.19**), part of the mesolimbocortical dopaminergic pathway illustrated in Figure 4.3, has been widely implicated in the perception of reward. If the dopaminergic pathway from the VTA to the nucleus accumbens serves as a reward system for a wide variety of experiences, then the addictive power of drugs may come from their artificial stimulation of this pathway. Acting on this assumption, Pilla et al. (1999) found that a weak DA agonist reduced cocaine craving in rats; perhaps the mild DA stimulation produced by the agonist filled in for the DA that would have been released by cocaine.

Similarly, socially dominant rhesus monkeys reportedly have increased numbers of dopamine D_2 receptors compared to subordinate monkeys, and they are less suscep-


(a)
Fluid out for analysis
Fluid in
Nucleus accumbens
Ventral tegmental area (VTA)
Medial forebrain bundle
Some of the dopamine released in the nucleus accumbens crosses the dialysis membrane and can be detected in the fluid flowing out.
Dialysis membrane
Dopamine

4.19 A Neural Pathway Implicated in Drug Abuse The microdialysis technique makes use of a small, permanently implanted probe to monitor neurochemical changes in awake, behaving animals. (*a*) A microdialysis probe inserted into the nucleus accumbens can detect changes in dopamine levels in response to drug administration. (*b*) Dopamine levels in the nucleus accumbens rise sharply in rats during self-administration (begins at arrow) of cocaine. (Part *b* after Pettit and Justice, 1991.)



tible to the reinforcing properties of cocaine than are the subordinates (Morgan et al., 2002). Interestingly, a single dose of cocaine is able to produce long-lasting changes in dopaminergic circuitry (Ungles et al., 2001); rapid changes like this are part of the process that allows addiction to start. Changes in dopaminergic activity may also potentiate memory processes that contribute to later drug hunger; it thus seems that dopamine participates in several parallel processes that collectively provide the motivation to repeatedly seek out the rewarding substance (Wise, 2004).

People differ in their vulnerability to drug abuse

Not everyone who uses an addictive drug becomes addicted. For example, very, very few hospitalized patients treated with opiates for pain relief go on to abuse opiates after leaving the hospital (Brownlee and Schrof, 1997). Of Vietnam War veterans who had used heroin overseas, only a minority relapsed to dependence within 3 years after their return (Robins and Slobodyan, 2003). The individual and environmental factors that account for this differential susceptibility are the subject of active investigation (Karch, 2006; M. Glantz and Pickens, 1992); they fall into several general categories:

- *Biological factors.* Sex is a significant variable; males are more likely to abuse drugs than are females. There is also evidence for genetic predisposition. For example, having a biological parent who suffers from alcoholism makes drug abuse more likely, even for children adopted away soon after birth (Cadoret et al., 1986); a tendency to use opiates and cocaine also appears to be heritable (Kendler et al., 2000). And in genetically modified mice, variation in a gene regulating the hormone response to stress contributes to increased intake of alcohol following stressful events (Sillaber et al., 2002); a similar mechanism could explain why some humans tip over into alcoholism at stressful times in their lives.
- *Personal characteristics.* Certain traits, such as aggressiveness and poor emotional control, are especially associated with drug abuse. Strong educational goals and maturity are associated with lower likelihood of drug abuse.
- *Family situation.* Family breakup, a poor relationship with parents, or the presence of an antisocial sibling are associated with drug abuse.
- *Environmental factors.* A high prevalence of drug use in the community, and especially in the peer group, predisposes an individual toward drug abuse. The effect of social factors is particularly marked with respect to the incidence of smoking: although seven of ten adult smokers in the United States say they want to quit, according to the U.S. Centers for Disease Control, their success in doing so directly correlates with race and educational status.

It is now clear that environmental stimuli—locations, social settings, sensory stimuli, and so on—can rapidly become strongly associated with the subjective effects of abused substances. These environmental stimuli can then become risk factors for deepening addiction or relapse: simply being in a setting where a person previously used drugs can trigger drug craving in that person (O'Brien et al., 1998). This phenomenon, termed **cue-induced drug use**, is not limited to longer-term users; in rats, exposure to environmental stimuli that were present *during their very first cocaine treatment* will effectively and persistently cue drug-seeking behavior later (Ciccocioppo et al., 2004). Evidence suggests that aspects of the strong cravings that occur during exposure to drug-associated environmental cues are mediated by the activation of a neural signaling system called the **extracellular signal–regulated kinase** (**ERK**) pathway, particularly in the central nucleus of the amygdala (Lu et al., 2005, 2006). The peptide **orexin**, found in neurons of the lateral hypothalamus and originally implicated in hunger for food (discussed in Chapter 13), may also contribute to drug hunger (G. C. Harris et al., 2005).

The greater the number of risk factors that apply, the more likely an individual will develop a substance abuse disorder (Brook et al., 1992). Furthermore, these risk factors do not necessarily operate independently; in some cases they interact to produce a more severe addiction that is resistant to interventions.

cue-induced drug use An increased likelihood to use a drug (especially an addictive drug) because of the presence of environmental stimuli that were present during previous use of the same drug.

extracellular signal–regulated kinase (ERK) An important intracellular signal transduction system that can be activated by many different events that affect the cell surface.

orexins A group of proteins expressed in the lateral hypothalamus that trigger feeding and have been implicated in narcolepsy.

Drug use, abuse, and dependence can be prevented or treated in multiple ways

Given the health and social costs of substance abuse, the development of effective treatment programs is a pressing concern. Many of those who become dependent are able to overcome their addiction without outside help: more than 90% of ex-smokers and about half of those who recover from alcoholism appear to have quit on their own (S. Cohen et al., 1989; Institute of Medicine, 1990). For those who require medical intervention, several categories of medication are available (Nathan and Gorman, 1998), including the following:

- *Drugs for detoxification.* Included in this category are benzodiazepines and drugs that suppress central adrenergic activity (e.g., clonidine). These drugs help reduce withdrawal symptoms during the early drug-free period.
- *Agonist or partial agonist analogs of the addictive drug.* Analogs partially activate the same mechanisms as the addictive drug, to help wean the individual. For example, the opioid receptor agonist methadone reduces heroin appetite and lessens withdrawal symptoms; similarly, nicotine patches provide reduced doses of the addictive compound, without the other harmful components of cigarette smoke.
- *Antagonists to the addictive drug.* Specific antagonists block the effects of an abused drug (e.g., the opiate antagonist naloxone blocks heroin's actions), but they also may produce harsh withdrawal symptoms.
- *Medications that alter drug metabolism.* Patients on disulfiram (trade name Antabuse) accumulate acetaldehyde, a toxic metabolite of alcohol that can be quite unpleasant. Drinking then produces illness that counteracts the rewarding aspects of alcohol abuse.
- *Reward-blocking medications.* Researchers are looking at ways to block the positive reward associated with drugs of abuse, primarily by using dopamine receptor blockers to reduce the activity of the mesolimbocortical dopamine reward system that we discussed earlier. One problem with this approach that must be overcome is the tendency of treatments to produce a general *anhedonia*, a generalized loss of pleasurable feelings.
- *Anticraving medications.* These medications reduce the appetite for the abused substance; for example, naltrexone (trade name ReVia) blocks the rewarding aspects of consuming alcohol or other abused substances, and acamprosate (trade name Campral) eases alcohol-associated withdrawal symptoms.

Could people be immunized against drug abuse? Vaccines against such drugs as cocaine, heroin, and nicotine have been synthesized, and they have improved to the point that they are now in clinical trials (Kantak, 2003). Here the strategy is to prompt the individual's immune system to produce antibodies that remove the targeted drugs from circulation before they ever reach the brain (Proksch et al., 2000). Alternatively, if a virus is used as a carrier to help penetrate the blood–brain barrier, antibodies can be delivered into the brain, where they will block cocaine's effects at a local level for up to two weeks (Carrera et al., 2004).

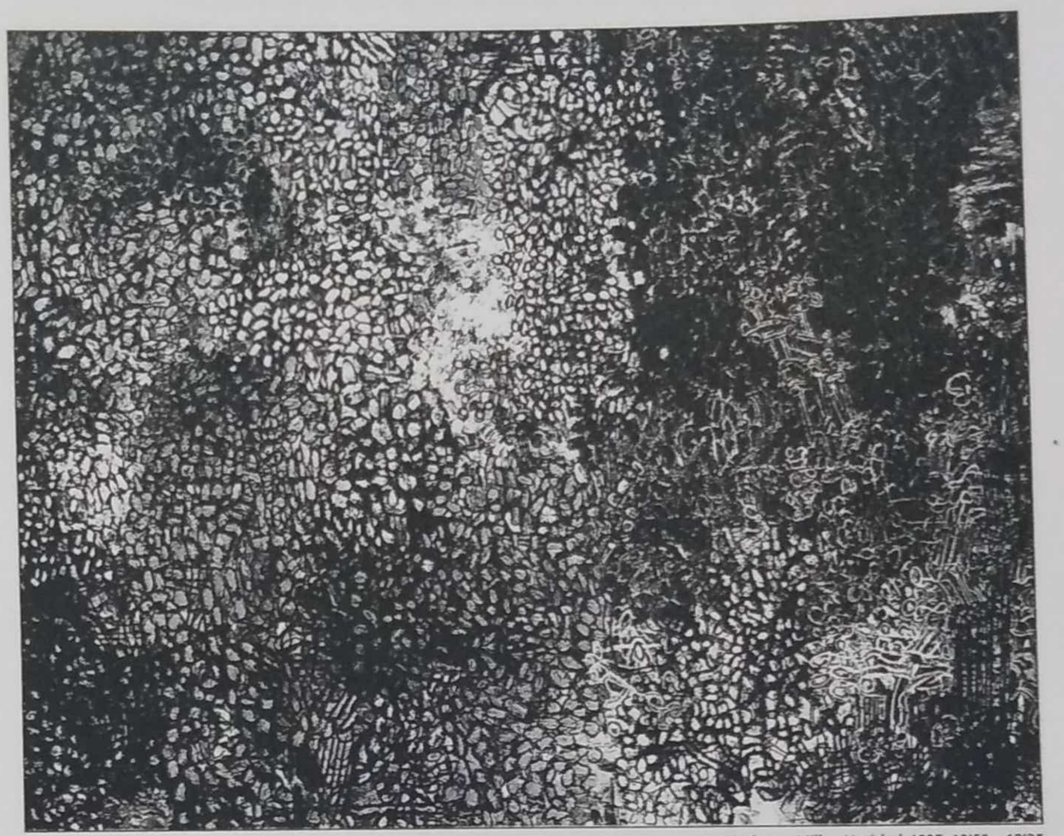
No single approach appears to be uniformly effective, and rates of relapse remain high. Research breakthroughs are therefore badly needed.

Summary

1. The major categories of neurotransmitters are amine, amino acid, peptide, and soluble gas neurotransmitters.
2. Because many drugs work by acting on receptor molecules, investigators search for the receptor molecules and for the endogenous substances that work on the receptors. A given neurotransmitter may normally bind several different subtypes of receptors.
3. A ligand is any substance that binds to a receptor. Agonists activate transmitter pathways, antagonists block transmitter pathways, and inverse agonists have active effects that are opposite to a transmitter's normal effects.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

CHAPTER 5



Nachume Miller, *Untitled*, 1995, 10'6" × 18'2"

CONTENTS

Hormones Act in a Great Variety of Ways throughout the Body 119

Hormones Act on a Wide Variety of Cellular Mechanisms 128

Each Endocrine Gland Secretes Specific Hormones 132

Hormones Affect Behavior in Many Different Ways 144

Hormonal and Neural Systems Interact to Produce Integrated Responses 146

Hormones and the Brain

Life-Threatening Lethargy

"Chuck's" mother finally became frightened and called 911. She told the emergency room staff that her son, a man in his 50s, had been lying on the sofa for weeks, watching TV and refusing to get up or do much else. He was sleepy most of the time, forgot appointments, and failed to finish chores that he started. This situation may sound familiar, but additional observations suggested that Chuck's problem was more than depression or mere laziness. His speech was slurred, his movements and heart rate were slow, and his cognitive abilities were so compromised that he couldn't name the month or the current president. In counting backward from 100 by sevens, he stalled at 93.

Chuck denied using drugs recreationally, and although he recalled taking an unknown medication previously, he was not currently taking any prescription drugs. Blood tests indicated no alcohol and no chronic infections that would affect the CNS; brain scans found no stroke, tumor, or other brain injuries. In the end, his diagnosis was suggested by one of the simplest and most familiar of tests: the knee jerk reflex in response to the tap of a rubber mallet. Chuck's knee jerk reflex was abnormally slow. A mysterious process appeared to be impeding the flow of information in his neurons, not only in the knee jerk circuitry but also, by extension, in the rest of his CNS (Jauhar, 2003).

What was wrong with Chuck?

The cells in our body use chemicals to communicate, including an extensive array of hormones. Changes in hormone levels can produce striking changes in the functioning of the nervous system. Cognitive abilities, emotions, our appetite for food or drink or sex, our aggressiveness or submissiveness, our care for children—the scope of hormonal influences on behavior is vast. Furthermore, hormones do more than influence adult behavior. Early in life, thyroid and sex hormones regulate brain development. Later in life, the changing outputs of endocrine glands and the body's changing sensitivity to hormones are prominent aspects of adolescence and aging.

In this chapter we consider the major hormones, their anatomical sources, their physiological actions, and their effects on behavior. This discussion sets the stage for topics in later chapters, such as hormonal effects in reproductive behavior (Chapter 12); feeding, drinking, and body maintenance (Chapter 13); and stress and emotion (Chapter 15).

Hormones Act in a Great Variety of Ways throughout the Body

Hormones (from the Greek *horman*, "to excite") are chemicals secreted by one group of cells and carried through the bloodstream to other parts of the body, where they act on specific target tissues to produce specific physiological effects. Many hormones are produced by **endocrine glands** (from the Greek *endon*, "within," and *krinein*, "to secrete"), so called because they release their hormones within the body. Endocrine glands are sometimes contrasted with **exocrine glands** (tear glands, salivary glands, sweat glands), which use ducts to secrete fluid outside the body (the Greek *exo* means "out").

hormone A chemical secreted by an endocrine gland that is conveyed by the bloodstream and regulates target organs or tissues.

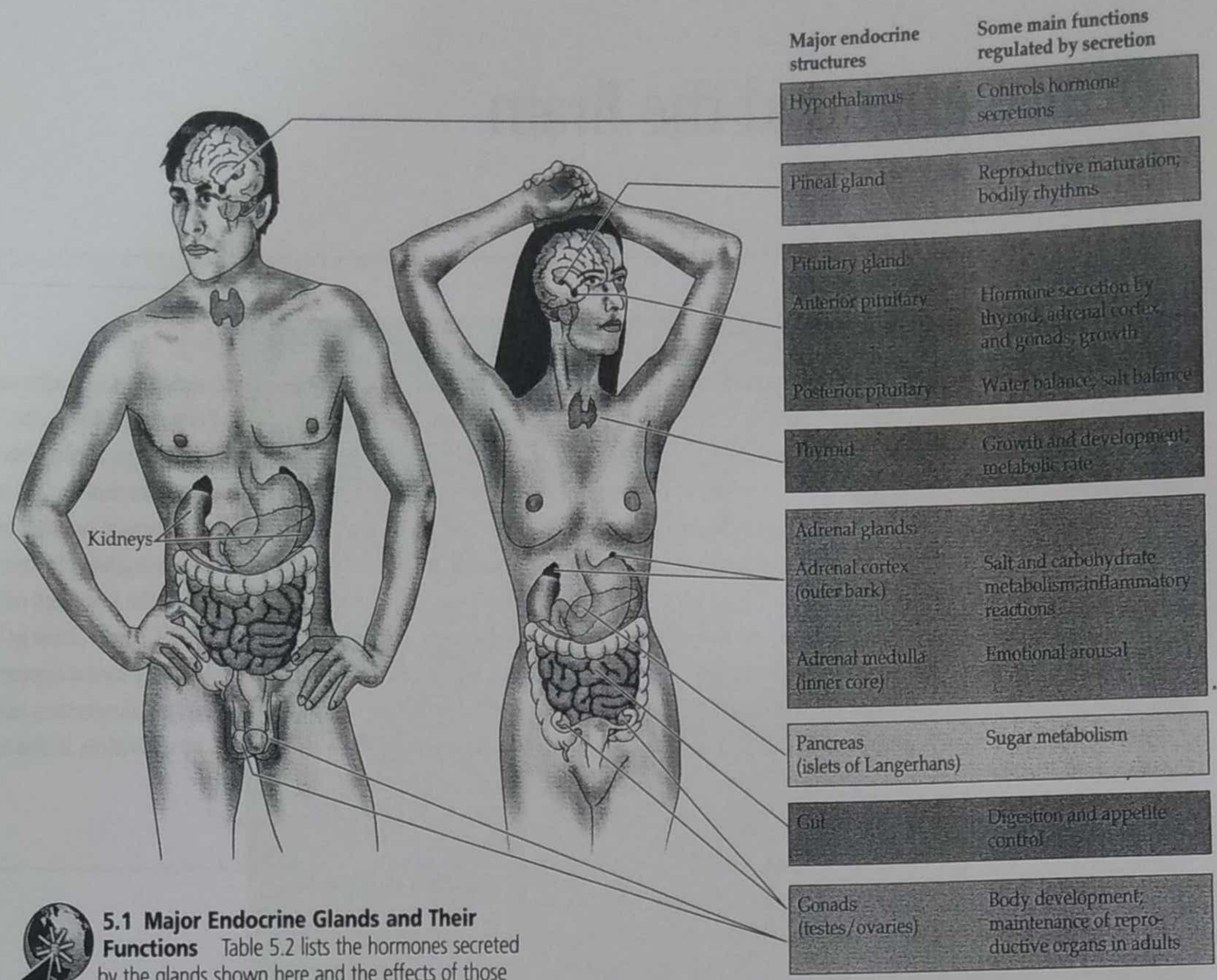
endocrine gland A gland that secretes products into the bloodstream to act on distant targets.

exocrine gland A gland whose secretions exit the body via ducts.

castration Removal of the gonads, usually the testes.

Our current understanding of hormones developed in stages

There's no doubt that the importance of hormones in various domains was anticipated in ancient civilization. In the fourth century BCE, Aristotle accurately described the effects of **castration** (removal of the testes) in birds, and he compared the behavioral and


Major endocrine structures
Some main functions regulated by secretion
Hypothalamus
Controls hormone secretions
Pineal gland
Reproductive maturation; bodily rhythms
Pituitary gland:
Anterior pituitary
Hormone secretion by thyroid, adrenal cortex, and gonads; growth
Posterior pituitary
Water balance; salt balance
Thyroid
Growth and development; metabolic rate
Adrenal glands:
Adrenal cortex (outer bark)
Salt and carbohydrate metabolism; inflammatory reactions
Adrenal medulla (inner core)
Emotional arousal
Pancreas (islets of Langerhans)
Sugar metabolism
Gut
Digestion and appetite control
Gonads (testes/ovaries)
Body development; maintenance of reproductive organs in adults
Kidneys

5.1 Major Endocrine Glands and Their Functions Table 5.2 lists the hormones secreted by the glands shown here and the effects of those hormones in the body.

bodily effects with those seen in eunuchs (castrated men). Some cultures considered endocrine glands to have special medicinal properties: by 100 ACE, Chinese scholars recommended eating dog testes to combat impotence. Perhaps this practice built on prehistoric agricultural knowledge of the physiological and behavioral changes that result from the castration of domestic livestock. Although no one knew what mechanism was involved, clearly the testes were important for the reproductive capacity and sexual characteristics of males.

The ancient Greeks emphasized body *humors*, or fluids, as an explanation of temperament and emotions. It was believed that these fluids—phlegm, blood, black bile, and yellow bile (also known as *choler*)—all interacted to produce health or disease. The notion of body fluids as the basis of human temperament lingers in our language in many now seldom used terms, such as *phlegmatic* ("sluggish"), *sanguine* ("cheerful"; *sanguis* is Latin for "blood"), *bilious* ("irritable"), and *choleric* ("hot-tempered") to describe personalities. We routinely refer to other people as *good-humored* or *ill-humored*.

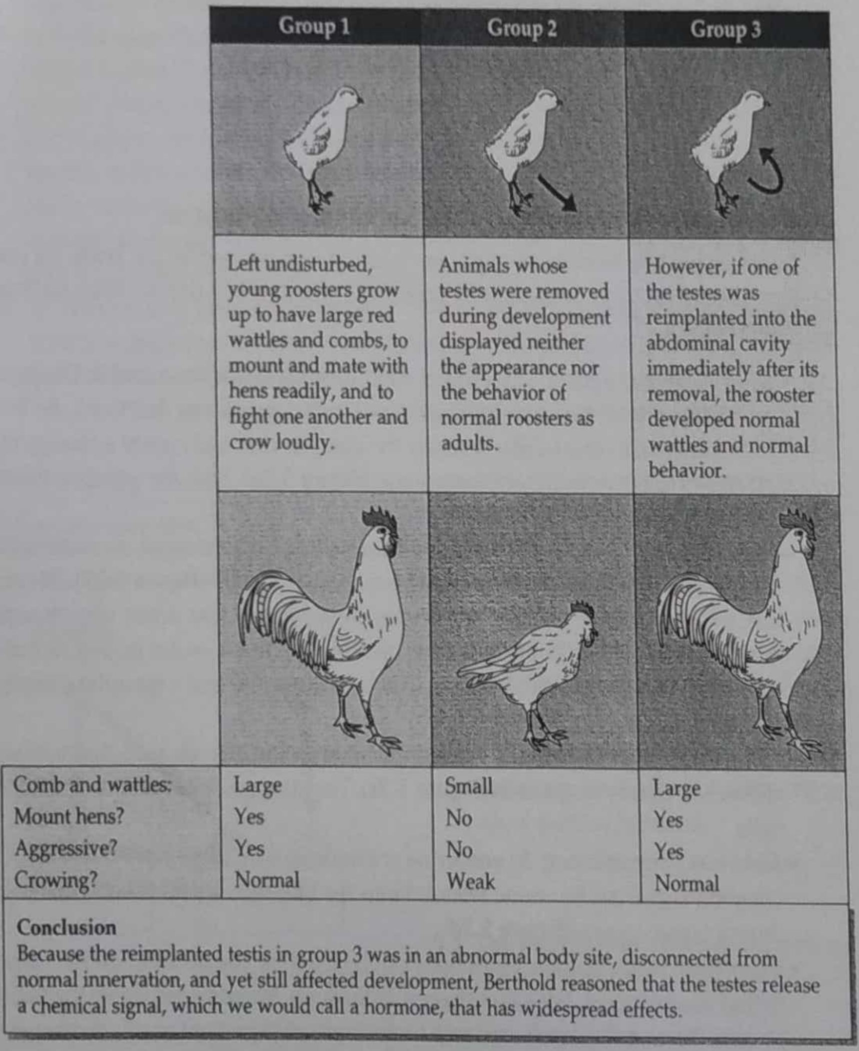
Today we know there are many more than four hormones. Endocrine glands come in a variety of sizes, shapes, and locations in the body (**Figure 5.1**). Although the endocrine glands and their hormones are important, the definition of *hormone* is more inclusive than it used to be, in the recognition that other tissues, such as the heart and kidneys, secrete hormones too. Even plants, which have no endocrine glands, use chemical signals that are considered to be hormones.

The first major endocrine experiment was carried out in 1849 by German physician Arnold Adolph Berthold (1803–1861), most likely replicating unpublished studies performed by John Hunter in England some 80 years previously (Sawin, 1996). When Berthold castrated juvenile roosters, they failed to develop normal reproductive behavior and secondary sexual characteristics, such as the rooster's comb, in adulthood (**Figure 5.2**). Berthold observed, however, that placing one testis into the body cavity of these castrates could preserve normal development of adult anatomy and behavior. These animals began crowing and showed the usual male sexual behaviors. Because the nerve supply to the testis had not been reestablished, Berthold concluded that the testes release a chemical into the blood that affects both male behavior and male body structures. Today we know that the testes make and release the hormone testosterone, which exerts these effects.

The French physiologist Claude Bernard (1813–1878) helped set the stage in the nineteenth century for the emergence of endocrinology as a science. Bernard stressed the importance of the internal environment ("internal milieu") in which cells exist and emphasized that this environment must be carefully regulated. He regarded a constant internal body environment as necessary for independent activity in the external environment.

This idea was later embedded in the concept of homeostasis advanced by American physiologist Walter B. Cannon (1871–1945) in the 1920s. **Homeostasis** is the maintenance of a relatively constant internal environment by an array of mechanisms in the body. Clinical and experimental observations starting in the late nineteenth century showed the importance of hormones from several glands—including the thyroid, the adrenal cortex, and the pituitary—for maintaining this constant environment inside our bodies.

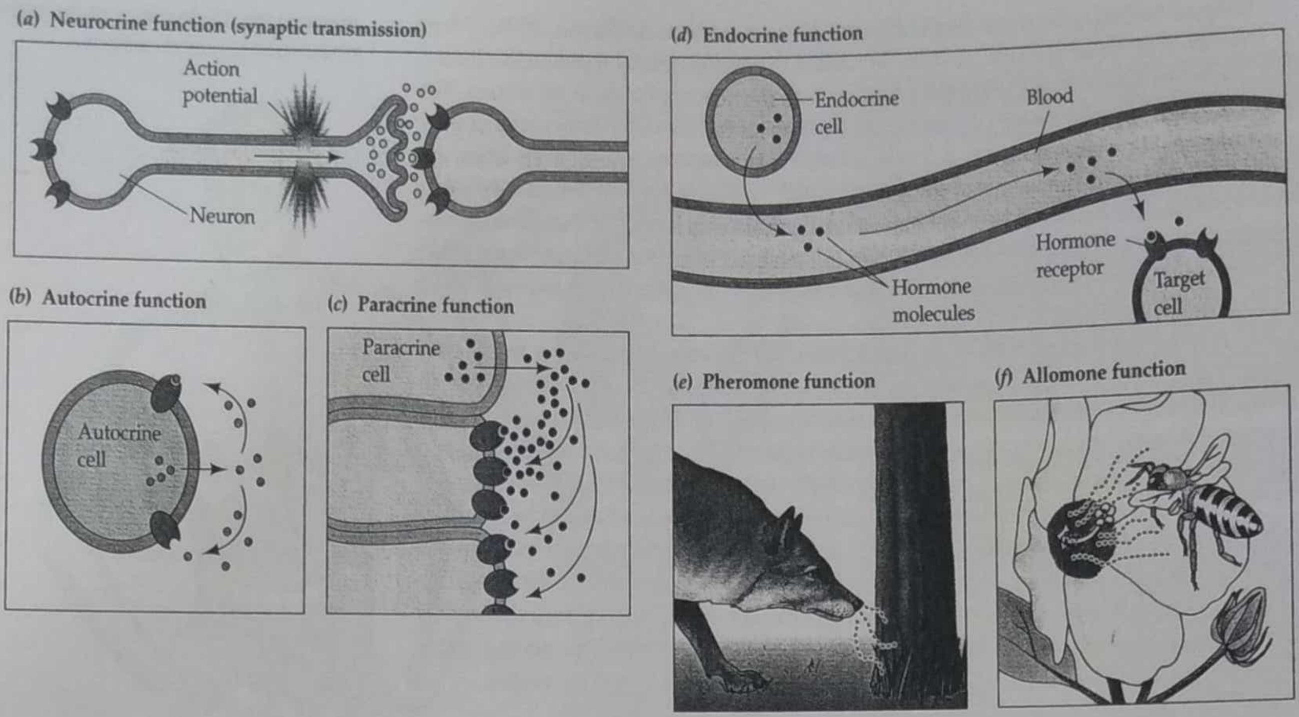
homeostasis The tendency for the internal environment to remain constant.



	Group 1	Group 2	Group 3
	Left undisturbed, young roosters grow up to have large red wattles and combs, to mount and mate with hens readily, and to fight one another and crow loudly.	Animals whose testes were removed during development displayed neither the appearance nor the behavior of normal roosters as adults.	However, if one of the testes was reimplanted into the abdominal cavity immediately after its removal, the rooster developed normal wattles and normal behavior.
Comb and wattles:	Large	Small	Large
Mount hens?	Yes	No	Yes
Aggressive?	Yes	No	Yes
Crowing?	Normal	Weak	Normal

Conclusion
Because the reimplanted testis in group 3 was in an abnormal body site, disconnected from normal innervation, and yet still affected development, Berthold reasoned that the testes release a chemical signal, which we would call a hormone, that has widespread effects.

5.2 The First Experiment in Behavioral Endocrinology Berthold's nineteenth-century experiment demonstrated the importance of hormones for behavior.


(a) Neurocrine function (synaptic transmission)
Action potential
Neuron
(b) Autocrine function
Autocrine cell
(c) Paracrine function
Paracrine cell
(d) Endocrine function
Endocrine cell
Blood
Hormone receptor
Hormone molecules
Target cell
(e) Pheromone function
(f) Allomone function

5.3 Chemical Communication Systems

Organisms use several types of chemical communication

By reviewing the several categories of chemical signals used by the body, we can see how hormonal communication by endocrine glands compares to other methods of communication:

- *Synaptic communication.* This form of communication was described in Chapters 3 and 4. In synaptic transmission (sometimes called **neurocrine** function), the released chemical signal diffuses across the synaptic cleft and causes a change in polarization of the postsynaptic membrane (**Figure 5.3*a***). Typically, synaptic transmitter function is highly localized.
- *Autocrine communication.* In **autocrine** communication, a released chemical acts on the releasing cell itself and thereby affects its own activity (**Figure 5.3*b***). For example, it is common for a neuron to contain autoreceptors that detect neurotransmitter molecules released by that neuron; the cell can thus monitor its own activity. In this case, the neurotransmitter serves both an autocrine and a synaptic communication function.
- *Paracrine communication.* In **paracrine** communication, the released chemical signal diffuses to nearby target cells (**Figure 5.3*c***). The strongest impact is on the nearest cells.
- *Endocrine communication.* In **endocrine** communication, as we have discussed, the chemical signal is a hormone released into the bloodstream to selectively affect distant target organs (**Figure 5.3*d***).
- *Pheromone communication.* Hormones can be used for communication not only within an individual, but also between individuals. **Pheromones** (from the Greek *pherein*, "to carry") are released into the outside environment to affect other individuals of the same species (**Figure 5.3*e***). For example, ants produce pheromones

neurocrine Referring to secretory functions of neurons, especially pertaining to synaptic transmission.

autocrine Referring to a signal that is secreted by a cell into its environment and that feeds back to the same cell.

paracrine Referring to cellular communication in which a chemical signal diffuses to nearby target cells through the intermediate extracellular space.

endocrine Referring to glands that release chemicals to the interior of the body. These glands secrete the principal hormones.

pheromone A chemical signal that is released outside the body of an animal and affects other members of the same species.

that communicate the presence of intruders in the nest, or identify the route to a rich food source (to the annoyance of picnickers everywhere). Dogs and wolves urinate on landmarks to designate their territory; other members of the species smell the pheromones in the urine and either respect or challenge the territory. In Chapters 9 and 12 we'll discuss pheromones in more detail.

- *Allomone communication.* Some chemical signals are released by members of one species to affect the behavior of individuals of *another* species (W. L. Brown, 1968). These substances are called **allomones** (from the Greek *allos*, "other"). Allomones can carry messages between animal species or from plants to animals (**Figures 5.3f and 5.4**). Flowers exude scented allomones to attract insects and birds in order to distribute pollen. And the bolas spider—nature's femme fatale—releases a moth sex pheromone to attract male moths to their doom (Eberhard, 1977; Haynes et al., 2002).

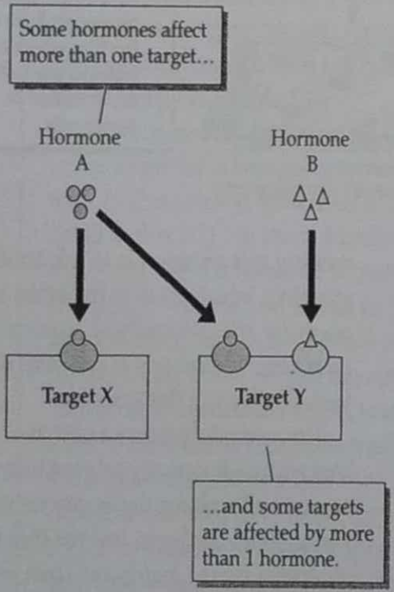
5.4 Scents and Sensibility Skunks produce what may be the best-known allomone of all.

allomone A chemical signal that is released outside the body by one species and affects the behavior of other species.

Hormone actions can be organized according to nine general principles

Although there are some exceptions, the following nine rules are general principles of hormone action:

1. Hormones frequently act in a *gradual* fashion, activating behavioral and physiological responses hours or weeks after entering the bloodstream. The changes may persist for days, weeks, or years after hormone release is over.
2. When hormones alter behavior, they tend to act by changing the intensity or probability of evoked behaviors, rather than acting as a switch to turn behaviors on or off regardless of context (**Box 5.1**).
3. Both the quantities and the types of hormones released are influenced by environmental factors. Therefore *the relationship between behavior and hormones is clearly reciprocal;* that is, hormones change behaviors and behaviors change hormone levels. For example, high levels of testosterone are related to aggression, and in some species, males who lose in aggressive encounters show a reduction in testosterone levels, while the winners in these bouts show little change in testosterone levels. This example shows the reciprocal relation between behavioral and somatic (body) events that we discussed in Chapter 1 (see Figure 1.2).
4. A hormone may have multiple effects on different cells, organs, and behaviors; conversely, a single type of behavior or physiological change can be affected by many different hormones (**Figure 5.5**).
5. Hormones are produced in small amounts and often are secreted in bursts. This *pulsatile* secretion pattern is sometimes crucial for the small amount of hormone to be effective.
6. The levels of many hormones vary rhythmically throughout the day, and many hormone systems are controlled by circadian "clocks" in the brain, as we'll see in Chapter 14.
7. Hormones interact; the effects of one hormone can be markedly changed by the actions of another hormone.


Some hormones affect more than one target...
Hormone A
Hormone B
Target X
Target Y
...and some targets are affected by more than 1 hormone.

5.5 The Multiplicity of Hormone Action A single hormone (hormone A in this illustration) may affect multiple target tissues in various locations throughout the body. Similarly, a single process or body organ (target Y here) may be sensitive to several hormones.

BOX 5.1 Techniques of Modern Behavioral Endocrinology

To establish that a particular hormone affects behavior, investigators usually begin with the type of experiment that Berthold performed in the nineteenth century: observing the behavior of the intact animal, then removing the endocrine gland and looking for a change in behavior (see Figure 5.2). Berthold was limited to this type of experiment, but modern scientists have many additional options available. Let's imagine that we're investigating a particular effect of hormones on behavior to see how we might proceed.

Which Hormones Affect Which Behaviors?

First we must carefully observe the behavior of several individuals, seeking ways to classify and quantify the different types of behavior and to place them in the context of the behavior of other individuals. For example, most adult male rats will try to mount and copulate with a receptive female placed in their cage. If the testes are removed from the male rat, he will eventually stop copulating with females. We know that one of the hormones produced by the testes is testosterone. Is it the loss of testosterone that causes the loss of male copulatory behavior?

To explore this question, we inject some synthetic testosterone into castrated males, and observe whether the copulatory behavior returns. (It does.) Another way to ask whether a steroid hormone is affecting a particular behavior is to examine the behavior of animals that lack the receptors for that steroid. We can delete the gene for a given hormone receptor, making a **knockout organism** (because the gene for the receptor has been "knocked out"), and ask which behaviors are different in the knockouts versus normal animals (see Box 7.3).

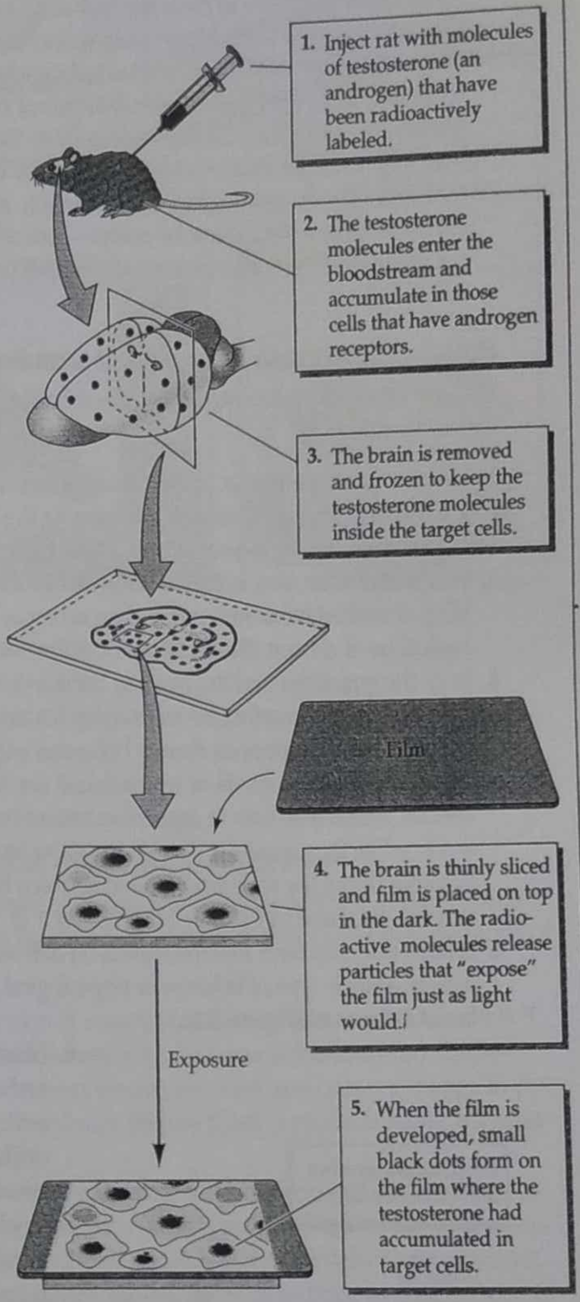
Next we might examine individual male rats and ask whether the ones that copulate a lot have more testosterone circulating in their blood than those who copulate only a little. To investigate this question, we measure individual differences in the amount of copulatory behavior, take a sample of blood from each individual, and measure levels of testosterone by using **radioimmunoassay (RIA)**, a technique using an antibody that binds to a particular hormone. By adding many such antibodies to each blood sample and measuring how many of the antibodies find a hormone molecule to bind, we can estimate the total number of molecules of the hormone per unit volume of blood.

It turns out that individual differences in the sexual behavior of normal male rats (and normal male humans) do *not* correlate with differences in testosterone levels in the blood. In both rats and humans, a drastic loss of testosterone, as after castration, results in a gradual decline in sexual behavior. All normal males, however, appear to make more than enough testosterone to maintain sexual behavior, so something else must modulate this behavior. In other words, the hormone acts in a permissive manner: it permits the display of the behavior, but something else determines how much of the behavior each individual exhibits.

Where Are the Target Cells?

What does testosterone do to permit sexual behavior? One step toward answering this question is to ask another question: which parts of the brain are normally affected by this hormone? We have several methods at our disposal for investigating this question.

First we might inject a castrated animal with radioactively labeled testosterone and wait for the hormone to accumulate in the brain regions that have receptors for the hormone. Then we

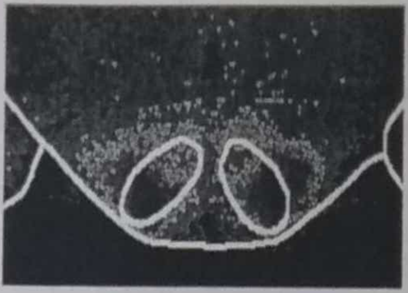


1. Inject rat with molecules of testosterone (an androgen) that have been radioactively labeled.
2. The testosterone molecules enter the bloodstream and accumulate in those cells that have androgen receptors.
3. The brain is removed and frozen to keep the testosterone molecules inside the target cells.
4. The brain is thinly sliced and film is placed on top in the dark. The radioactive molecules release particles that "expose" the film just as light would.
5. When the film is developed, small black dots form on the film where the testosterone had accumulated in target cells.

(A) Steps in steroid autoradiography

BOX 5.1 (continued)

(B) An autoradiogram showing that spinal motoneurons (purple cell profiles) accumulate radioactive testosterone (small dots)



(C) An oxytocin autoradiogram showing the concentration of oxytocin receptors in the ventromedial hypothalamus (oval outlines)

(D) Immunocytochemistry revealing cells with nuclei that contain androgen receptors (dark circles), to which testosterone can bind. The somata of these neurons have been labeled with the tracers fluorogold (white) and fluororuby (red).

can sacrifice the animal, remove the brain, freeze it, cut thin sections from it, and place the thin sections on photographic film. Radioactive emissions from the tissue expose the film, revealing which brain regions had accumulated the most labeled testosterone. This method is known as **autoradiography** because the tissue "takes its own picture" with radioactivity (Figure A).

When the labeled hormone is a steroid like testosterone, the radioactivity accumulates in the nuclei of neurons and leaves small black specks on the film (Figure B). When the radiolabeled hormone is a protein hormone such as oxytocin, the radioactivity accumulates in the membranes of cells and appears in particular layers of the brain. Computers can generate color maps that highlight regions with high densities of receptors (Figure C).

Another method for detecting hormone receptors is **immunocytochemistry**. In this method (described in more detail in Box 2.1), we use antibodies that recognize the hormone receptor (Figure D). This method allows us to map the distribution of hormone receptors in the brain. We put the antibodies on slices of brain tissue, wait for them to bind to the receptors, wash off the unbound antibodies, and use chemical methods to visualize the antibodies by creating a tiny dark spot at each one. When the antibodies recognize a steroid receptor, chemical reactions cause a dark coloration in the nuclei of target brain cells. We can also use **in situ hybridization** (see Box 2.1) to look for the neurons that make the mRNA for the steroid receptor. Because these cells make the transcript for the receptor, they are likely to possess the receptor protein itself.

What Happens at the Target Cells?

Once we have used autoradiography, immunocytochemistry, or in situ hybridization (or, better yet, all three) to identify brain regions that have receptors for the hormone, those regions become candidates for the places at which the hormone works to change behavior. Now we can take castrated males and implant tiny pellets of testosterone into one of those brain regions. We use RIA to ensure that the pellets are small enough that they have no effect on hormone levels in the blood. Then we ask whether the small implant in that brain region restores the behavior. If not, then in other animals we can implant pellets in a different region or try placing implants in a combination of brain sites.

It turns out that such implants can restore male sexual behavior in rats only if they are placed in the medial preoptic area (mPOA) of the hypothalamus. Thus we have found so far that testosterone does something to the mPOA to permit individual males to display sexual behavior. Now we can examine the mPOA in detail to learn what changes in the anatomy, physiology, or protein production of this region are caused by testosterone. We have more or less caught up to modern-day scientists who work on this very question. Some of the preliminary answers suggested by their research will be discussed in Chapter 12. (Figure C courtesy of Bruce McEwen; D courtesy of Cynthia Jordan.)

knockout organism An individual in which a particular gene has been disabled by an experimenter.

radioimmunoassay (RIA) A technique that uses antibodies to measure the concentration of a substance, such as a hormone, in blood.

autoradiography A histological technique that shows the distribution of radioactive chemicals in tissues.

immunocytochemistry (ICC) A method for detecting a particular protein in tissues in which (1) an antibody recognizes and binds to the protein and (2) chemical methods are then used to leave a visible reaction product around each antibody.

in situ hybridization A method for detecting particular RNA transcripts in tissue sections by providing a nucleotide probe that is complementary to, and will therefore hybridize with, the transcript of interest.

neurosecretory cell or neuroendocrine cell A neuron that releases hormones into local or systemic circulation.

neuropeptide A peptide that is used by neurons for signaling.

neuromodulator A substance that influences the activity of synaptic transmitters.

8. The chemical structure of a given hormone is similar in all vertebrates, but the *functions* served by that hormone can vary across species.
9. Hormones can affect only cells possessing a receptor protein that recognizes the hormone and alters cell function. Among different vertebrates, the same brain regions often possess the same hormone receptors.

Neural and hormonal communications are similar in some ways and different in others

Neurotransmission—chemical communication between neurons—and hormonal communication are both secretory events, and they seem similar in several ways (**Figure 5.6**). For example, the neuron produces particular transmitter chemicals and stores them for later release, just as an endocrine gland stores its hormones for secretion. Another similarity between the two systems is that both neurotransmitters and hormones, upon binding to receptor molecules on the cell surface, often activate second messengers within the target cell to bring about changes in metabolism, membrane potentials, and other cellular functions. Moreover, the same chemicals act as second messengers in both the nervous and the endocrine systems.

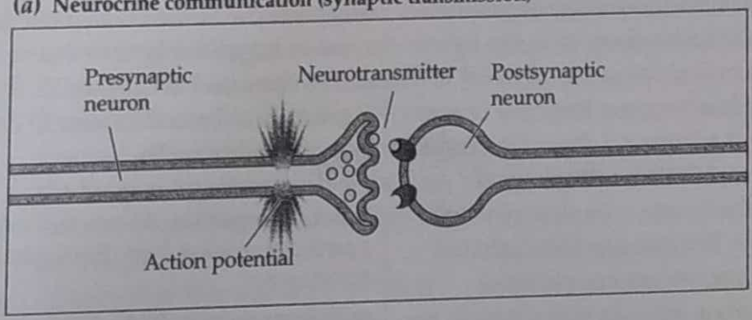
Similarities between neuronal and hormonal communication are especially exemplified by the **neurosecretory** (or **neuroendocrine**) **cells** of the hypothalamus (see Figure 5.6*c*). These cells are neurons in almost every way except at their axon terminals, where instead of releasing transmitter into a synapse, they release hormones into the bloodstream. It is thus difficult to draw a firm line between neurons and endocrine cells. In fact, some investigators believe that the endocrine glands may have evolved from neurosecretory cells (Norman and Litwack, 1987).

Findings that certain chemicals in vertebrates—either hormonal peptides or **neuropeptides** (peptides used by neurons)—are also found in single-celled organisms suggest that both the nervous system and the endocrine system are derived from chemical communication systems in our remote single-celled ancestors (LeRoith et al., 1992). Some neuropeptides are used as neurotransmitters, but sometimes neuropeptides act as **neuromodulators** (see Chapter 4), substances that alter the reactivity of cells to specific transmitters. The effects of neuromodulators (compared to neurotransmitters) tend to arise more slowly and last longer. So neuromodulators are something of a blend of neurotransmitter (because they're released into synapses) and hormone (because they act gradually).

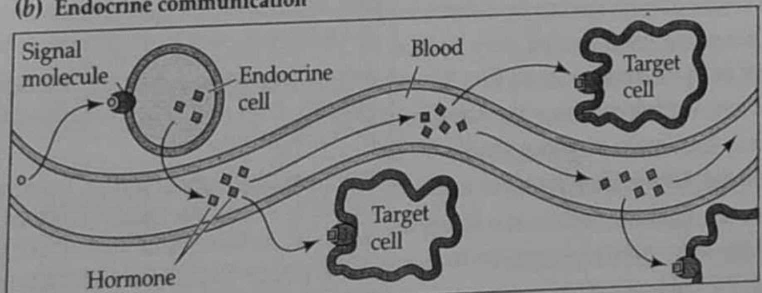
Despite the many similarities between neural and hormonal communication, the two systems differ in five basic ways:

1. *Neural communication* works somewhat like a telephone system: messages travel over fixed channels to

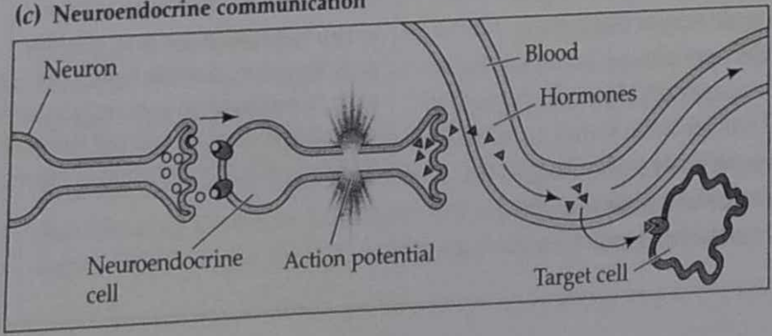
(*a*) **Neurocrine communication (synaptic transmission)**



(*b*) **Endocrine communication**



(*c*) **Neuroendocrine communication**



5.6 Neuroendocrine Cells Blend Neuronal and Endocrine Mechanisms (*a*) Neurons communicate with other neurons or with muscle cells or glands, and signal transmission is determined by the pattern of anatomical connections. (*b*) Endocrine signals are transmitted through the bloodstream and are recognized by appropriate receptors in specific locations in the body. (*c*) Neuroendocrine (neurosecretory) cells are the interface between neurons and endocrine glands. They receive neural signals from other neurons and secrete a hormone into the bloodstream. In this way electrical signals are converted into hormonal signals.

precise destinations. The anatomical connections between neurons determine the source and destination of information. In contrast, *hormonal communication* works more like a radio broadcasting system: many different endocrine messages spread throughout the body and can then be picked up by scattered cells that have receptors for them. Some hormones broadcast rather locally; for instance, the hypothalamus sends hormones only a few millimeters through the blood vessels to the anterior pituitary gland. Other hormones broadcast throughout the body, but because cells in only a particular organ have the proper receptors, these hormones influence only that organ.

2. Whereas neural messages are rapid and are measured in milliseconds, hormonal messages are slower and are measured in seconds and minutes.
3. The distance traveled by the chemical messengers differs enormously in the two cases; the synaptic cleft is only about 30 nm wide, but hormones may travel more than a meter to reach the target organ.
4. Most neural messages are *digital*, consisting of sequences of all-or-none action potentials. Hormonal messages are *analog*—that is, graded in strength.
5. Neural and hormonal communication also differs in terms of voluntary control. You cannot consciously change secretion of hormones in the way that you can voluntarily lift your arm, blink your eyelids, or perform many other acts under neuromuscular control. This distinction between neural and hormonal systems, however, is not absolute. Some muscular activities—such as heart rate or intestinal action—are not generally subject to conscious control, even though they are regulated by the nervous system.

protein or peptide hormones A class of hormones, molecules of which consist of a string of amino acids.

amine hormones A class of hormones, each composed of a single amino acid that has been modified into a related molecule, such as melatonin or epinephrine.

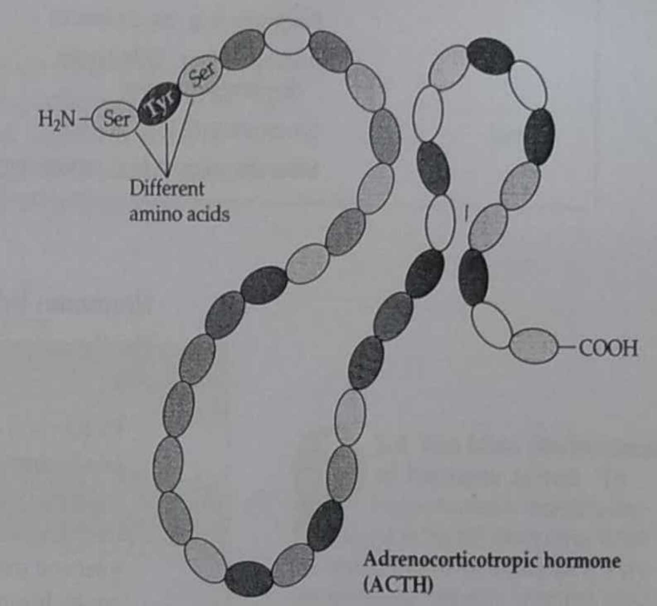
steroid hormones A class of hormones, each of which is composed of four interconnected rings of carbon atoms.

Hormones can be classified by chemical structure

Most hormones fall into one of three categories: protein hormones, amine hormones, or steroid hormones. Like any other protein, a **protein hormone** is composed of a string of amino acids (**Figure 5.7*a***). (Recall that a peptide is simply a small protein—i.e., a short string of amino acids.) Different protein hormones consist of different combinations of amino acids. **Amine hormones** are smaller and simpler, consisting of a modified version of a single amino acid (hence their alias, *monoamine* hormones) (**Figure 5.7*b***). **Steroid hormones** are derivatives of cholesterol and thus share its structure of four rings of carbon atoms (**Figure 5.7*c***). Different steroid hormones vary in the number and kinds of atoms attached to the rings. Steroids dissolve readily in lipids, so they can cross through membranes easily (recall from Chapter 2 that the cell membrane is a lipid bilayer).

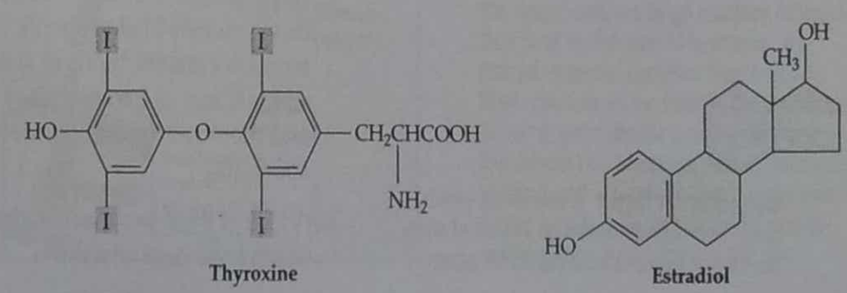
The distinction between protein or amine hormones and steroid hormones is important because these hor-

(*a*) Protein hormone



(*b*) Amine hormone

(*c*) Steroid hormone



5.7 Chemical Structures of the Three Main Hormone Types (a) Protein hormones consist of strings of amino acids. If the string is short, as it is in adrenocorticotropic hormone (ACTH), it may be referred to as a *peptide hormone*. (b) Amine hormones, such as thyroxine, are modified single amino acids. (c) Steroid hormones, such as estradiol, are derived from cholesterol and consist of four interconnected rings of carbon atoms, to which are attached different numbers and types of atoms.

mone classes interact with different types of receptor mechanisms. **Table 5.1** gives examples of each class of hormones.

TABLE 5.1 Major Classes of Hormones

Class	Hormone
PROTEIN HORMONES	Adrenocorticotropic hormone (ACTH)
	Follicle-stimulating hormone (FSH)
	Luteinizing hormone (LH)
	Thyroid-stimulating hormone (TSH)
	Growth hormone (GH)
	Prolactin
	Insulin
	Glucagon
	Oxytocin
	Vasopressin (arginine vasopressin, AVP; antidiuretic hormone, ADH)
	Releasing hormones, such as: Corticotropin-releasing hormone (CRH) Gonadotropin-releasing hormone (GnRH)
AMINE HORMONES	Epinephrine (adrenaline)
	Norepinephrine (NE)
	Thyroid hormones
	Melatonin
STEROID HORMONES	
Gonadal	Estrogens (e.g., estradiol)
	Progestins (e.g., progesterone)
	Androgens (e.g., testosterone, dihydrotestosterone)
Adrenal	Glucocorticoids (e.g., cortisol)
	Mineralocorticoids (e.g., aldosterone)

Hormones Act on a Wide Variety of Cellular Mechanisms

In later chapters we will be considering the effects of specific hormones on behavior. In preparation for that discussion, let's look briefly at three aspects of hormonal activity: the effects of hormones on cells, the mechanisms by which hormones exercise these effects, and the regulation of hormone secretion.

Hormones affect cells by influencing their growth and activity

By influencing cells in various tissues and organs, hormones affect many everyday behaviors in humans and other animals. Hormones exert these far-reaching effects by (1) promoting the proliferation, growth, and differentiation of cells; and (2) modulating cell activity. Early developmental processes are promoted by various hormones—for example, the thyroid hormones. Without these hormones, fewer cells are produced in the brain, and mental development is stunted. Although cells proliferate and differentiate mainly during early development in the brain, hormones cause cells in some organs to divide and grow at later stages of life too. For example, sex hormones cause secondary sexual characteristics to appear during adolescence: breasts and broadening of the hips in women, and facial hair and enlargement of the Adam's apple in men.

In cells that are already differentiated, hormones can modulate the rate of function. Thyroid hormones and insulin, for instance, regulate the metabolic activity of most of the cells in the human body. Other hormones modulate activity in certain types of cells. For example, luteinizing hormone (a hormone from the anterior pituitary gland) promotes the secretion of sex hormones by the testes and ovaries.

Hormones initiate actions by binding to receptor molecules

The three classes of hormones exert their influences on target organs in two different ways:

1. Protein and amine hormones bind to specific receptors (proteins that recognize only one hormone or class of hormones). Such receptors are usually found *on the surface* of target cell membranes and, when stimulated by the appropriate hormone, cause the release of a second messenger in the cell. (As we saw in Chapter 3, the release of a second messenger can also be caused by some synaptic transmitters.) Protein and amine hormones exert their effects by using this mechanism to alter proteins and processes within the target cell.
2. As we mentioned earlier, steroid hormones easily pass through cell membranes, so they generally bind to specific receptor proteins located *inside* the cell. The steroid–receptor complex binds to specific regions of the DNA in the nucleus of the cell, where it acts as a **transcription factor**, controlling the expression of specific genes, and thereby increasing or decreasing the rate of production of proteins (see the appendix).

Let's look at these two main modes of action in a little more detail and examine the ways in which hormones affect cells.

transcription factor A substance which binds to recognition sites on DNA and alters the rate of expression of particular genes.

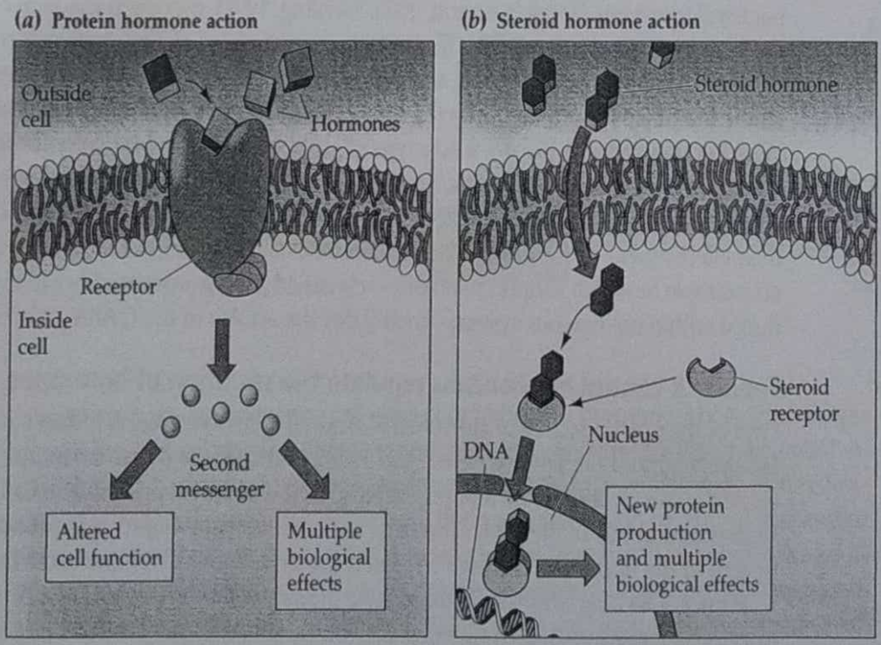
PROTEIN AND AMINE HORMONES ACT RAPIDLY What determines whether a cell responds to a particular protein hormone? Only those cells that produce the appropriate receptor proteins for a hormone and insert them into the membrane can respond to that hormone. As we saw with neurotransmitter receptors in Chapters 3 and 4, the receptor protein spans the cellular membrane. When a hormone binds to the extracellular portion of the receptor, the receptor molecule changes its overall shape. The alteration in the intracellular portion of the receptor then changes the internal chemistry of the cell, most often by activating a second messenger (**Figure 5.8a**).

One second-messenger compound in particular—cyclic adenosine monophosphate (cyclic AMP or cAMP)—transmits the messages of many of the peptide and amine hormones. It may seem surprising that the same second messenger can mediate the effects of many different hormones, but a change in cAMP levels can cause many different outcomes, depending on which cells are affected, on which part of a cell is affected, and on the prior biochemical activity inside the cell. Other widespread second-messenger compounds include cyclic guanosine monophosphate (cGMP) and phosphoinositides.

The specificity of hormonal effects is determined in large part by the selectivity of receptors. Only a minority of cells produce the receptor that recognizes and reacts to a particular hormone, and thus only those cells can respond to it. For example, adrenocorticotropic hormone (ACTH) interacts with receptors on the membranes of cells in the adrenal cortex, and in these cells an increase in cAMP leads to the synthesis and release of other hormones.

Protein hormones usually act relatively rapidly, within seconds to minutes. (Although rapid for a hormone, this action is much slower than neural activity.) There can also be prolonged effects. For example, ACTH promotes the proliferation and growth of adrenal cortical cells, thereby increasing the long-term capacity to sustain production of their hormones. A cell may increase or decrease the number of hormone receptors it makes, and these changes are sometimes referred to as up-regulation and down-regulation, respectively.

STEROID HORMONES ACT SLOWLY Steroid hormones typically act more slowly than protein or amine hormones, requiring hours to take effect. The specificity of action of steroid hormones is determined by the receptors that reside *inside* target cells. These receptors are truly ancient, in an evolutionary sense; evidence suggests that estrogen receptors first arose in primordial invertebrate species 600 to 1000 million years ago


(*a*) Protein hormone action

(*b*) Steroid hormone action

5.8 Two Main Mechanisms of Hormone Action (*a*) Protein hormone receptors are found in the cell membrane. When the hormone binds to the receptor, a second-messenger system is activated, which affects various cellular processes. (*b*) Steroid hormones diffuse passively into cells. Inside the target cells are large receptor molecules that bind to the steroid hormone. The steroid–receptor complex then binds to DNA, causing an increase in the production of some gene products and a decrease in the production of others. This is the mechanism by which steroids exert a genomic effect, which is distinct from the nongenomic effects mentioned in the text.

(Thornton et al., 2003), probably through exploitation of even more-ancient mechanisms (Bridgham et al., 2006).

Steroid hormones pass in and out of many cells in which they have no effect. If appropriate receptor proteins are inside, however, these receptors bind to the hormone, and the receptor–steroid complex then binds to DNA, so the complexes become concentrated in the nuclei of target cells (**Figure 5.8*b***). Thus, as Box 5.1 describes, we can study where a steroid hormone is active by injecting radioactively tagged molecules of the steroid and observing where they accumulate. For example, tagged estradiol accumulates not only in the reproductive tract (as you might expect), but also in the nuclei of some neurons throughout the hypothalamus.

By altering protein production, steroids have slow but long-lasting effects on the development or adult function of cells. We will discuss such effects of steroids further in Chapter 12. Within our DNA is a large "superfamily" of steroid receptor genes (Ribeiro et al., 1995), and some steroids act on more than one receptor. For example, a second estrogen **receptor isoform** (steroid receptor subtype) has been described and named estrogen receptor β (Kuiper et al., 1996) to distinguish it from the previously discovered estrogen receptor α. The brain contains both types of estrogen receptors—one more prominent in some regions, the other more prominent in others. Scientists are trying to tease apart their separate effects on behavior.

Simple possession of appropriate steroid receptors is not enough to ensure that a given neuron will respond to the presence of that particular steroid hormone. Cells make a wide variety of **steroid receptor cofactors** that may be required, along with the bound steroid receptors, in order for the cell to respond. Furthermore, the nature of the response may be determined by the type of cofactor present: two different cells containing the same steroid receptors may respond quite differently to the steroid hormone if they are producing different steroid receptor cofactors (Tetel, 2000). These cofactors thus determine which genes will be regulated when the steroid hormone and its receptor reach the nucleus. For example, two of the best-known cofactors, **steroid receptor cofactor-1** (**SRC-1**) and **CREB-binding protein** (**CBP**) play a role in sexual dimorphism in the brain (Auger et al., 2002) and in the spinal cord (Ranson et al., 2003). Blocking these cofactors from functioning prevents estrogen and progesterone from having their usual effects on the sexual behavior of female rats (Molenda-Figueira et al., 2006).

Steroids may be able to affect cells through mechanisms other than the classic nuclear steroid receptor. For example, estradiol, in addition to its slow, long-lasting action on gene expression, can have a rapid, brief effect on some neurons without affecting gene expression. This rapid **nongenomic effect** of steroids involves a separate class of receptors in the neuronal *membrane* (Toran-Allerand, 2005; Wehling, 1997), modulating neural excitability. Similarly, androgenic steroids like testosterone can have effects that are too rapid to involve the transcription of genes, and appear to involve androgen receptors localized in axons and other sites, distant from the cell nucleus and its DNA (DonCarlos et al., 2006). Whether these actions involve a new type of androgen receptor, or a novel action of the already known androgen receptor, remains to be determined. Alternatively, steroids can work rapidly by interacting with receptors for other signaling molecules and changing their effectiveness—a function known as **allosteric modulation**. In Chapter 4 we discussed an example in which allopregnanolone—classified as a **neurosteroid** because it is produced within the nervous system—modulates the activity of the $GABA_A$ receptor.

Feedback control mechanisms regulate the secretion of hormones

One of the major features of almost all hormonal systems is that they don't just manufacture a hormone; they also detect and evaluate the effects of the hormone. Thus, secretion is usually monitored and regulated so that the rate is appropriate to ongoing activities and needs of the body. The basic control used is a **negative feedback** system: output of the hormone *feeds back* to inhibit the drive for more of that same hormone.

Figure 5.9a diagrams the simplest kind of system that regulates hormones: an endocrine cell releases a hormone that acts on target cells, but the same hormone also feeds back to inhibit the gland that released it. This is an autocrine response.

receptor isoform A version of a receptor protein (in this context, a hormone receptor) with slight differences in structure that give it different functional properties. Conceptually similar to receptor subtypes.

steroid receptor cofactors Proteins that affect the cell's response when a steroid hormone binds its receptor.

steroid receptor cofactor-1 (SCR-1) A transcription co-factor that, when present along with molecules of steroid hormone, helps determine the response of the cell to the hormone.

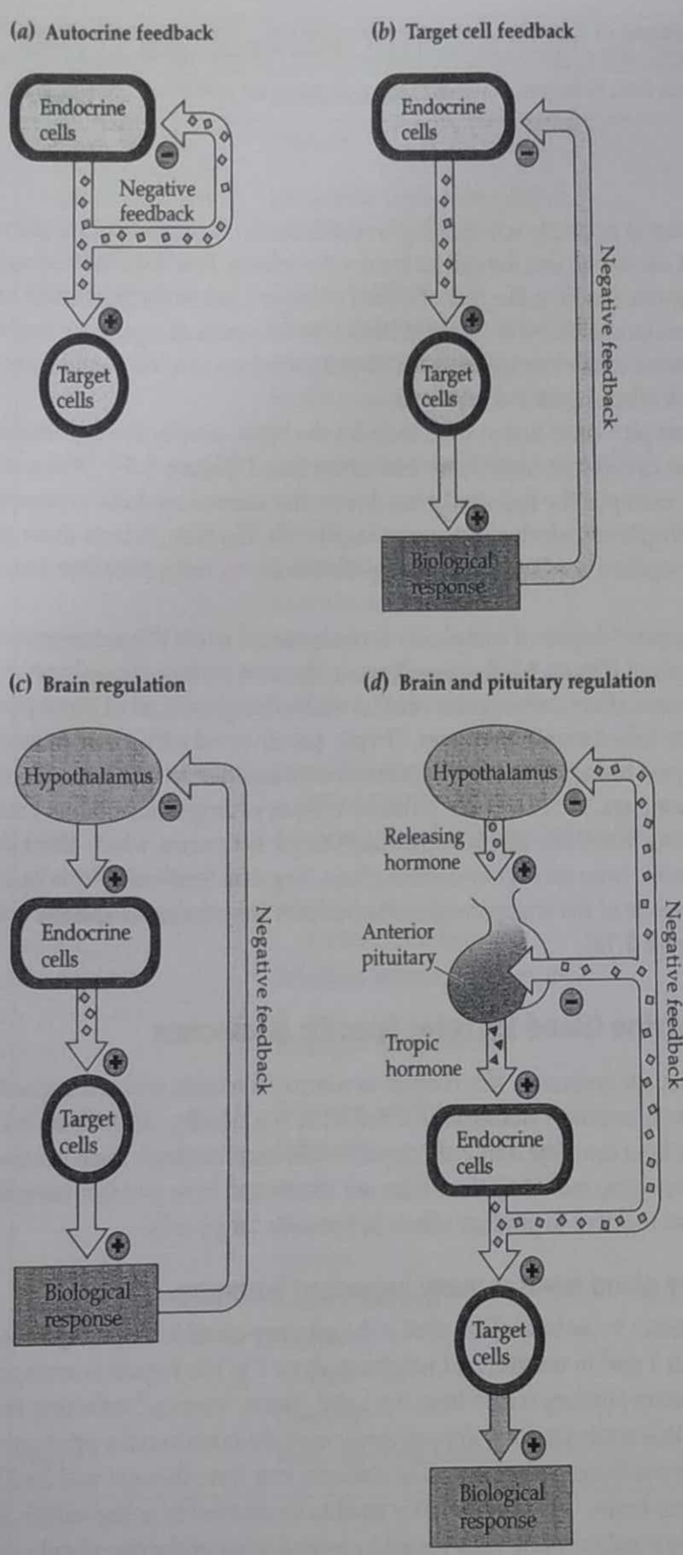
CREB-binding protein (CBP) A transcriptional cofactor that works with CREB (camp-responsive element binding protein) to regulate gene expression.

nongenomic effect An effect of a steroid hormone that is not mediated by direct changes in gene expression.

allosteric modulation Alteration of the actions of a protein—such as a receptor—by binding to an alternative location on the protein, distinct from the primary recognition site.

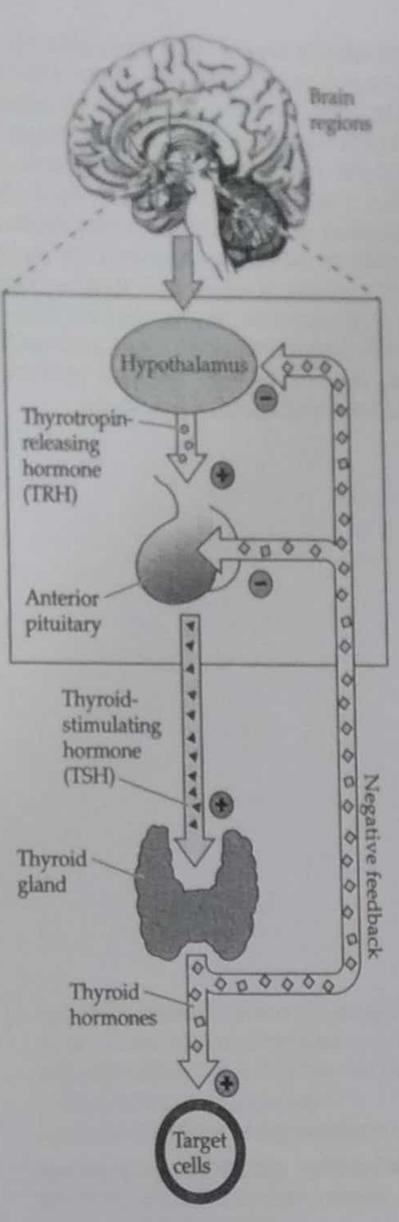
neurosteroids Steroids produced in the brain.

negative feedback The property by which some of the output of a system feeds back to reduce the effect of input signals.


(a) Autocrine feedback
Endocrine cells
Negative feedback
Target cells
(b) Target cell feedback
Endocrine cells
Target cells
Biological response
Negative feedback
(c) Brain regulation
Hypothalamus
Endocrine cells
Target cells
Biological response
Negative feedback
(d) Brain and pituitary regulation
Hypothalamus
Releasing hormone
Anterior pituitary
Tropic hormone
Endocrine cells
Target cells
Biological response
Negative feedback

5.9 Endocrine Feedback Loops (*a*) In the simplest type of negative feedback control, an endocrine gland releases a hormone that not only acts on a target, but also feeds back in an autocrine fashion to inhibit further hormone secretion. (*b*) The hormone from the endocrine gland acts on target cells to produce a specific set of biological effects. The consequences of these effects may be detected by the endocrine gland, inhibiting further hormone release. (*c*) In many feedback systems the brain becomes involved. The hypothalamic region drives the endocrine gland via either neural or hormonal signals. The target organ signals the brain to inhibit this drive. (*d*) Highly complex feedback mechanisms involve the hypothalamus and the anterior pituitary, as well as the endocrine gland. Feedback is regulated by a variety of hormones via multiple routes.

In other cases, the endocrine cell reacts not to its own hormone, but to the biological response that the hormone elicits from the target cells (**Figure 5.9*b***). If the initial effect is too small, additional hormone is released; if the effect is sufficient, no further hormone is released. For example, we release the hormone insulin to control the level of glucose circulating in our blood. After a meal, glucose from the food enters the bloodstream, causing insulin to be released from the pancreas. The insulin causes glucose to enter muscle and fat cells. As the level of glucose in the blood falls, the pancreas secretes less insulin, so a balance tends to be maintained.



5.10 An Example of Complex Endocrine Regulation The brain funnels information to the hypothalamus, which then controls the anterior pituitary, which in turn stimulates the thyroid gland. Note that three hormones and at least four cell groups are interacting in this instance.

Thus, insulin is normally self-limiting: as more insulin is secreted, more glucose is pulled out of circulation and the call for insulin diminishes. This negative feedback action of a hormone system is like that of a thermostat, and just as the thermostat can be set to different temperatures at different times, the set points of a person's endocrine feedback systems can be changed to meet varying circumstances. We'll encounter negative feedback effects again in Chapter 13.

A more complex endocrine system includes the brain, usually the hypothalamus, as part of the circuit that controls an endocrine gland (**Figure 5.9c**). When we are alarmed, for example, the hypothalamus directs the adrenal medulla to secrete the hormone epinephrine, which affects many target cells. The brain detects these effects and exerts negative feedback on the hypothalamus to reduce further hormone output.

An even greater degree of complexity is encountered when the anterior pituitary becomes involved (**Figure 5.9*d***). As we'll see in the next section, several anterior pituitary hormones affect the secretion of other endocrine glands; all of these pituitary hormones are called **tropic hormones**. (*Tropic*, pronounced with a long *o* as in *toe*, means "directed toward.") The hypothalamus uses another set of hormones, called **releasing hormones**, to control the pituitary release of tropic hormones. Thus the brain's releasing hormones affect the pituitary's tropic hormones, which affect the release of hormone from another endocrine gland. Negative feedback in this case goes from the hormone of the endocrine gland to both the hypothalamus and the anterior pituitary (**Figure 5.10**).

Each Endocrine Gland Secretes Specific Hormones

We will restrict our account in this chapter to some of the main endocrine glands because a thorough treatment would fill an entire book (e.g., Hadley, 2000). **Table 5.2** gives a fuller but far from complete listing of hormones and their functions. Keep in mind that most hormones have more functions than are mentioned here and that several hormones may act together to produce effects in the same target cells.

The pituitary gland releases many important hormones

Resting in a socket in the base of the skull is the **pituitary gland** (or **hypophysis**; see Figure 5.1), about 1 cm^3 in volume and weighing about 1 g. The hypothalamus sits just above it. The term *pituitary* comes from the Latin *pituita*, "mucus," reflecting the outmoded belief that waste products dripped down from the brain into the pituitary, which secreted them out through the nose. (The ancients may have thought you could literally sneeze your brains out!) The pituitary used to be referred to as the *master gland*, a reference to its regulatory role with regard to several other endocrine glands. But this gland is itself enslaved by the hypothalamus above it, as we'll see.

The pituitary gland consists of two main parts: the **anterior pituitary** (or **adenohypophysis**) and the **posterior pituitary** (or **neurohypophysis**). The anterior and posterior pituitary develop from different embryonic tissues and are completely separate in function. The pituitary is connected to the hypothalamus by a thin piece of tissue called the **pituitary stalk** or **infundibulum** (see Figure 5.11). The stalk contains many axons and is richly supplied with blood vessels. The axons extend only to the posterior pituitary, which we will consider next. The blood vessels, as we will see later, transmit information exclusively to the anterior pituitary.

tropic hormones A class of anterior pituitary hormones that affect the secretion of other endocrine glands.

releasing hormones A class of hormones, produced in the hypothalamus, that traverse the hypothalamic–pituitary portal system to control the pituitary's release of tropic hormones.

pituitary gland or hypophysis A small, complex endocrine gland located in a socket at the base of the skull.

anterior pituitary or adenohypophysis The front lobe of the pituitary gland; secretes tropic hormones.

posterior pituitary or neurohypophysis The rear division of the pituitary gland.

pituitary stalk or infundibulum A thin piece of tissue that connects the pituitary gland to the hypothalamus.

TABLE 5.2 Main Endocrine Glands, Their Hormone Products, and Principal Effects of the Hormones

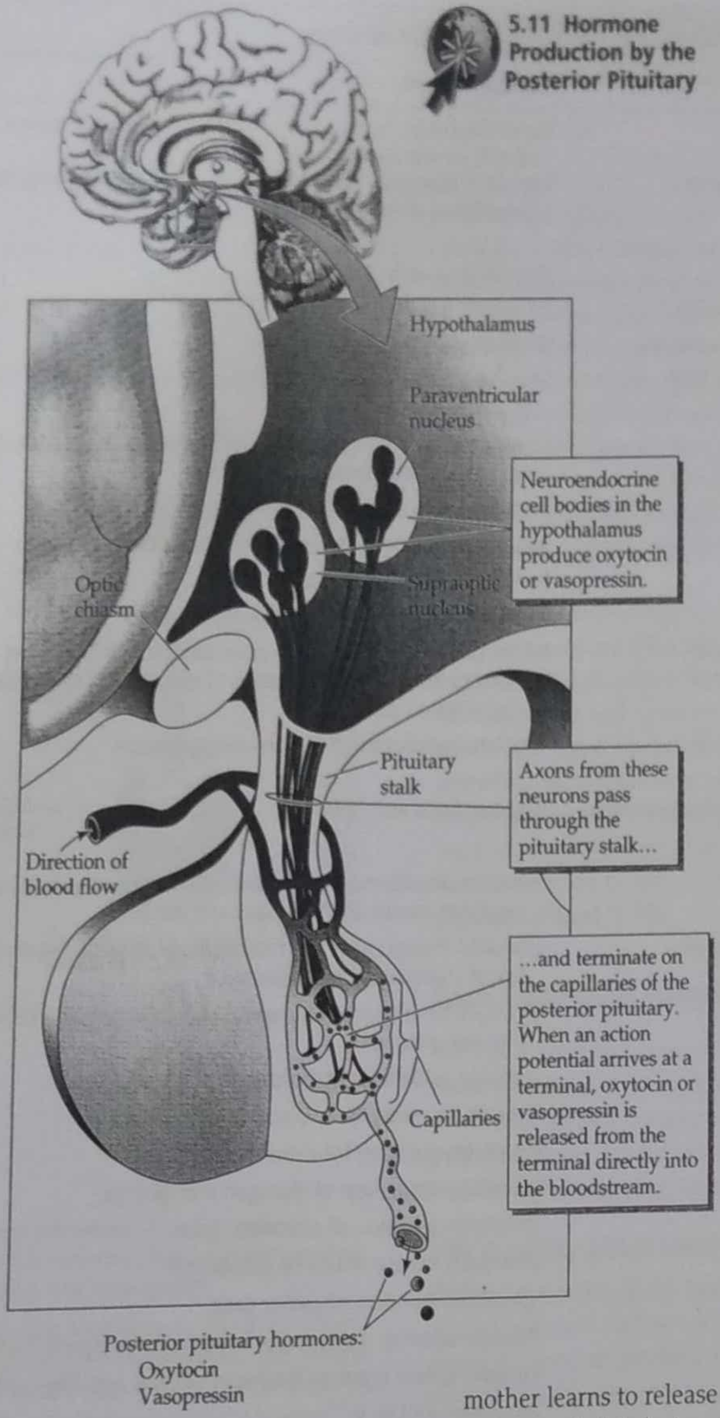
Gland	Hormones	Principal effects
Posterior pituitary (storage organ for certain hormones produced by hypothalamus)	Oxytocin	Stimulates contraction of uterine muscles; stimulates release of milk by mammary glands
	Vasopressin (AVP), or antidiuretic hormone (ADH)	Stimulates increased water reabsorption by kidneys; stimulates constriction of blood vessels
Anterior pituitary	Growth hormone (GH)	Stimulates growth
	Thyroid-stimulating hormone (TSH)	Stimulates the thyroid
	Adrenocorticotropic hormone (ACTH)	Stimulates the adrenal cortex
	Follicle-stimulating hormone (FSH)	Stimulates growth of ovarian follicles and of seminiferous tubules of the testes
	Luteinizing hormone (LH)	Stimulates conversion of follicles into corpora lutea; stimulates secretion of sex hormones by gonads
	Prolactin	Stimulates milk secretion by mammary glands
Hypothalamus	Releasing hormones	Regulate hormone secretion by anterior pituitary
	Oxytocin; vasopressin	*See under* Posterior pituitary
Pineal	Melatonin	Regulates seasonal changes; regulates puberty
Adrenal cortex	Glucocorticoids (corticosterone, cortisol, hydrocortisone, etc.)	Inhibit incorporation of amino acids into protein in muscle; stimulate formation and storage of glycogen; help maintain normal blood sugar level
	Mineralocorticoids (aldosterone, deoxycorticosterone, etc.)	Regulate metabolism of sodium and potassium
	Sex hormones (especially androstenedione)	Regulate facial and body hair
Gonads		
Testes	Androgens (testosterone, dihydrotestosterone, etc.)	Stimulate development and maintenance of male primary and secondary sexual characteristics and behavior
Ovaries	Estrogens (estradiol, estrone, etc.)	Stimulate development and maintenance of female secondary sexual characteristics and behavior
	Progestins (progesterone)	Stimulate female secondary sexual characteristics and behavior; maintain pregnancy
Thyroid	Thyroxine; triiodothyronine	Stimulate oxidative metabolism
	Calcitonin	Prevents excessive rise in blood calcium
Pancreas	Insulin	Stimulates glycogen formation and storage
	Glucagon	Stimulates conversion of glycogen into glucose
Stomach	Secretin	Stimulates secretion of pancreatic juice
	Cholecystokinin (CCK)	Stimulates release of bile by gallbladder
	Gastrin	Stimulates secretion of gastric juice
	Ghrelin	Provides appetite signal to the hypothalamus appetite controller
	Obestatin	Provides satiety signal to the hypothalamus appetite controller
Heart	Atrial natriuretic peptide	Promotes salt loss in urine

THE POSTERIOR PITUITARY The posterior pituitary gland secretes two principal hormones: **oxytocin** and **arginine vasopressin** (**AVP**), often called just **vasopressin**. Neurons in various hypothalamic nuclei, especially the supraoptic nucleus and the paraventricular nucleus, synthesize these two hormones and transport them along their axons to the axon terminals (**Figure 5.11**). Action potentials in these hypothalamic neurosecretory cells travel down the axons in the pituitary stalk and reach the axon terminals in the posterior pituitary, causing release of the hormone from the terminals into the rich

oxytocin A hormone, released from the posterior pituitary, that triggers milk letdown in the nursing female.

arginine vasopressin (AVP) or vasopressin A peptide hormone from the posterior pituitary that promotes water conservation.

5.11 Hormone Production by the Posterior Pituitary



Neuroendocrine cell bodies in the hypothalamus produce oxytocin or vasopressin.

Axons from these neurons pass through the pituitary stalk...

...and terminate on the capillaries of the posterior pituitary. When an action potential arrives at a terminal, oxytocin or vasopressin is released from the terminal directly into the bloodstream.

vascular bed of the neurohypophysis. The axon terminals abut capillaries (small blood vessels), allowing the hormone to enter circulation immediately.

Some of the signals that activate the nerve cells of the supraoptic and paraventricular nuclei are related to thirst and water regulation, which we will discuss in Chapter 13. Secretion of vasopressin increases blood pressure by causing blood vessels to contract. Vasopressin also inhibits the formation of urine, so it is sometimes called *antidiuretic hormone (ADH)* (a *diuretic* is a food or drug that promotes urination). This action of vasopressin helps conserve water. In fact, the major physiological role of vasopressin is its potent antidiuretic activity; it exerts this effect with less than one-thousandth of the dose needed to alter blood pressure.

Oxytocin is involved in many aspects of reproductive and parental behavior. One of its functions is to stimulate the contractions of the uterus in childbirth (the word *oxytocin* is derived from the Greek *oxys*, "rapid," and *tokos*, "childbirth"). Injections of oxytocin (or the synthetic version, Pitocin) are frequently used in medical settings to induce or accelerate labor and delivery. .

Oxytocin also triggers the **milk letdown reflex**, the contraction of mammary gland cells that ejects milk into the breast ducts. This phenomenon exemplifies the reciprocal relationship between behavior and hormone release. When an infant or young animal first begins to suckle, the arrival of milk at the nipple is delayed by 30 to 60 s. This delay is caused by the sequence of steps that precedes letdown. Stimulation of the nipple activates receptors in the skin, which transmit this information through a chain of neurons and synapses to hypothalamic cells that contain oxytocin. Once these cells have been sufficiently stimulated, the hormone is released from the posterior pituitary and travels via the bloodstream to the mammary glands, where it produces a contraction of the tissues storing milk, making the milk available at the nipple (**Figure 5.12**).

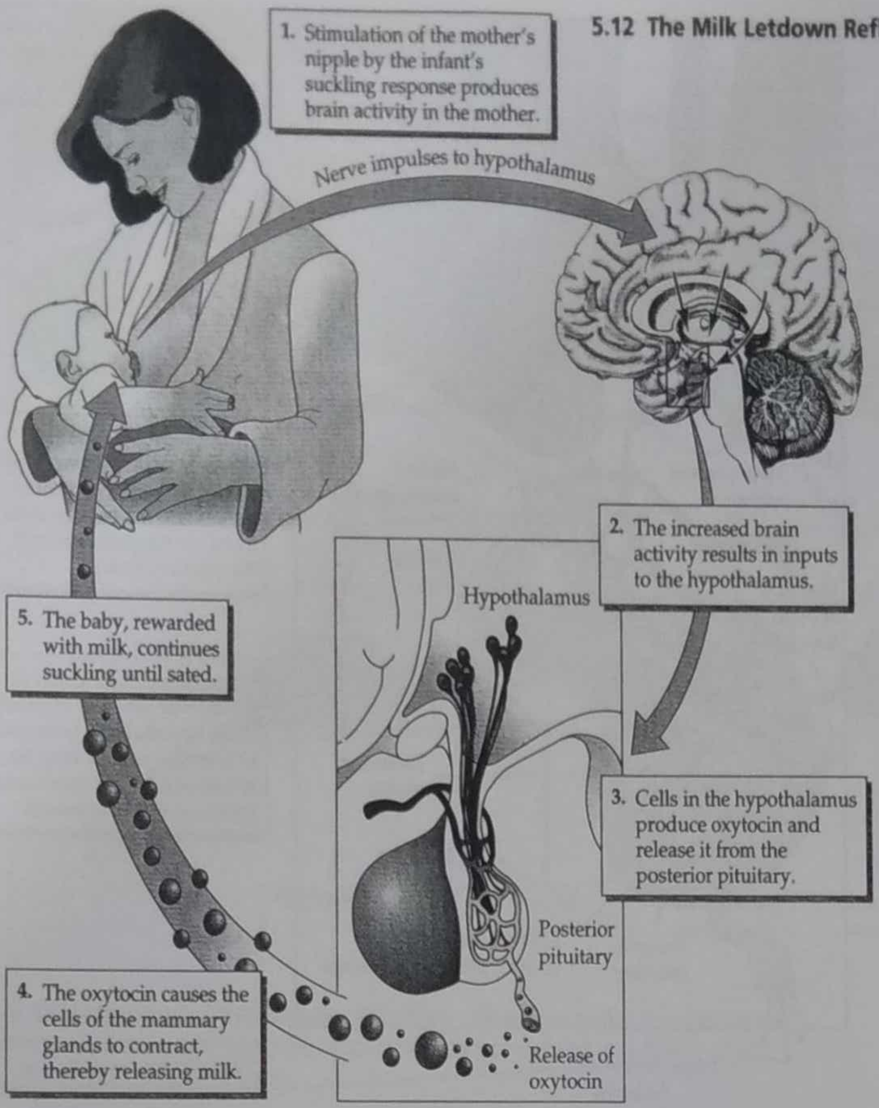
For mothers, this reflex response to suckling frequently becomes conditioned to baby cries so that milk appears promptly at the start of nursing. Because the mother learns to release oxytocin *before* the suckling begins, sometimes the cries of someone else's baby in public trigger an inconvenient release of milk. Oxytocin and vasopressin also serve as neurotransmitters from hypothalamic cells (**Figure 5.13**), projecting widely through the nervous system. Oxytocin and vasopressin have been implicated in social behaviors, as we'll discuss near the end of this chapter.

THE ANTERIOR PITUITARY Different cells of the anterior lobe of the pituitary synthesize and release different tropic hormones, which we'll discuss in the next section. Secretion of these tropic hormones, however, is under the control of releasing hormones, as mentioned earlier. We will briefly note some of the properties of these hypothalamic releasing hormones before further considering anterior pituitary actions.

Hypothalamic releasing hormones govern the anterior pituitary

The neurons that synthesize the different releasing hormones are neuroendocrine cells residing in various regions of the hypothalamus. The axons of these neuroendocrine cells

milk letdown reflex The reflexive release of milk in response to suckling, or to stimuli associated with suckling.


1. Stimulation of the mother's nipple by the infant's suckling response produces brain activity in the mother.
Nerve impulses to hypothalamus
2. The increased brain activity results in inputs to the hypothalamus.
Hypothalamus
3. Cells in the hypothalamus produce oxytocin and release it from the posterior pituitary.
Posterior pituitary
Release of oxytocin
4. The oxytocin causes the cells of the mammary glands to contract, thereby releasing milk.
5. The baby, rewarded with milk, continues suckling until sated.

5.12 The Milk Letdown Reflex

converge on the **median eminence**, just above the pituitary stalk. This region contains an elaborate profusion of blood vessels that form the **hypophyseal portal system**. Here, in response to inputs from the rest of the brain, the axon terminals of the hypothalamic neuroendocrine cells secrete their releasing hormones into the local bloodstream (**Figure 5.14**).

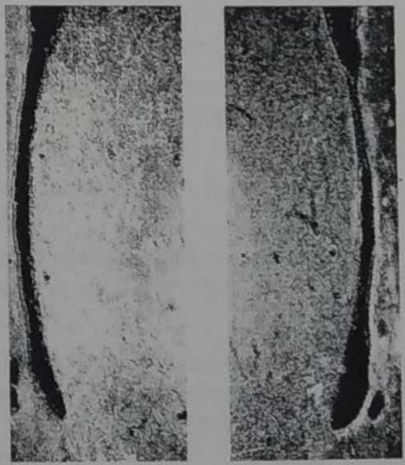
Blood carries the various releasing hormones only a very short distance, into the anterior pituitary. The rate at which releasing hormones arrive at their target cells in the anterior pituitary controls the rate at which the anterior pituitary cells, in turn, release their tropic hormones into the general circulation. These tropic hormones then regulate the activity of major endocrine organs throughout the body.

Hypothalamic control applies to all the anterior pituitary hormones. The hypothalamic neuroendocrine cells that synthesize the releasing hormones are themselves subject to two kinds of influences:

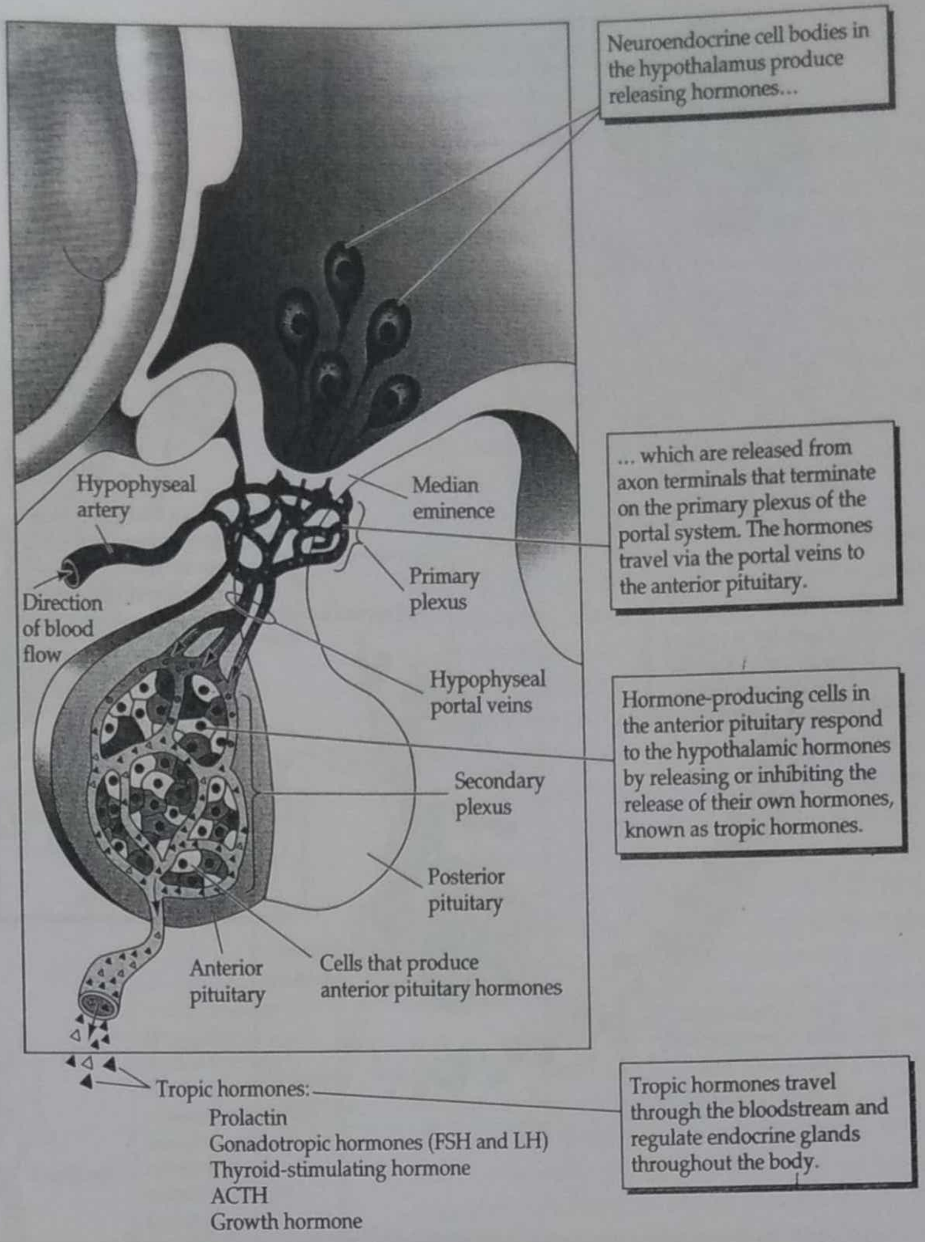
1. They are directly affected by *circulating messages*, such as other hormones (especially hormones that have themselves been secreted in response to tropic hormones), and

median eminence Midline feature on the base of the brain marking the point at which the infundibulum exits from the the hypothalamus to connect to the pituitary. Contains elements of the hypophyseal portal system.

hypophyseal portal system A duplex system of capillaries spanning between the neurosecretory cells of the hypothalamus and the secretory tissue of the anterior pituitary.



5.13 Vasopressin Can Serve as a Neurotransmitter Revealed here by immunocytochemistry are vasopressin-filled axonal fibers (yellow) in the septum of intact (*left*) and castrated (*right*) male rats. (Courtesy of Geert DeVries.)


Hypophyseal artery
Direction of blood flow
Median eminence
Primary plexus
Hypophyseal portal veins
Secondary plexus
Posterior pituitary
Anterior pituitary
Cells that produce anterior pituitary hormones
Tropic hormones:
Prolactin
Gonadotropic hormones (FSH and LH)
Thyroid-stimulating hormone
ACTH
Growth hormone

Neuroendocrine cell bodies in the hypothalamus produce releasing hormones...

... which are released from axon terminals that terminate on the primary plexus of the portal system. The hormones travel via the portal veins to the anterior pituitary.

Hormone-producing cells in the anterior pituitary respond to the hypothalamic hormones by releasing or inhibiting the release of their own hormones, known as tropic hormones.

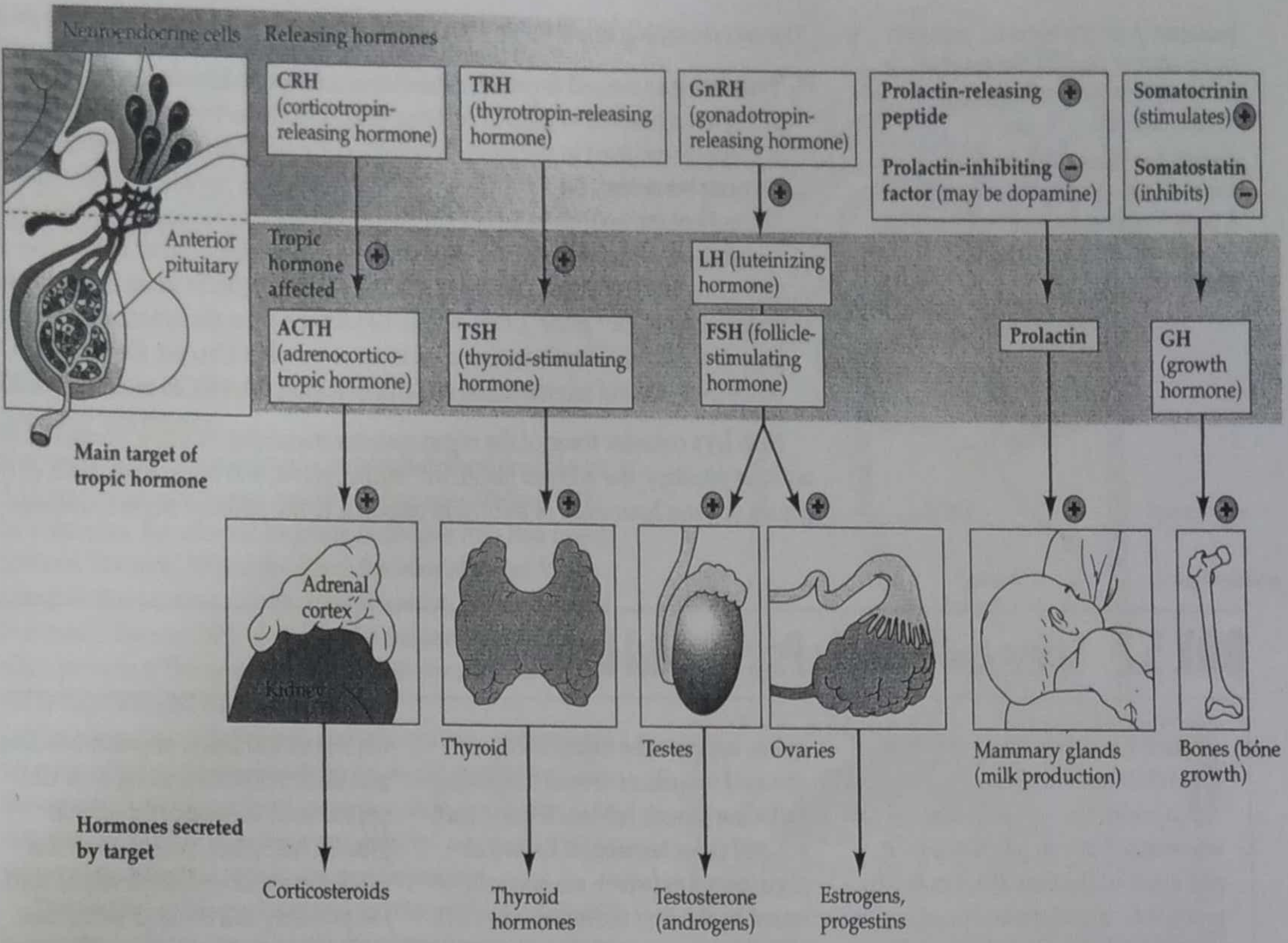
Tropic hormones travel through the bloodstream and regulate endocrine glands throughout the body.

5.14 Hormone Release by the Anterior Pituitary

by blood sugar and products of the immune system. The hypothalamus is not shielded by the blood–brain barrier (see Chapter 2) to the same extent that other brain regions are, which makes it possible for a wide variety of blood-borne material to access the hypothalamic neuroendocrine cells.

2. They receive *synaptic inputs* (either excitatory or inhibitory) from many other brain regions. A wide range of neural signals, reflecting both internal and external events, can thereby influence the endocrine system. As a result, hormone actions can be coordinated with ongoing events, and conditioning (learning) can alter endocrine status. We saw an example of such influence in our discussion of the milk letdown reflex, and we'll see other examples throughout the book.

The hypothalamic releasing-hormone system therefore exerts high-level control over endocrine organs throughout the body and provides a route by which brain activity is translated into hormonal action. Cutting the pituitary stalk interrupts the portal blood vessels and the flow of releasing hormones, leading to profound atrophy of the pituitary and major hormonal disruptions.


Neuroendocrine cells
Releasing hormones
CRH (corticotropin-releasing hormone)
TRH (thyrotropin-releasing hormone)
GnRH (gonadotropin-releasing hormone)
Prolactin-releasing peptide +
Prolactin-inhibiting factor (may be dopamine) −
Somatocrinin (stimulates) +
Somatostatin (inhibits) −
Anterior pituitary
Tropic hormone affected
LH (luteinizing hormone)
ACTH (adrenocorticotropic hormone)
TSH (thyroid-stimulating hormone)
FSH (follicle-stimulating hormone)
Prolactin
GH (growth hormone)
Main target of tropic hormone
Adrenal cortex
Kidney
Thyroid
Testes
Ovaries
Mammary glands (milk production)
Bones (bone growth)
Hormones secreted by target
Corticosteroids
Thyroid hormones
Testosterone (androgens)
Estrogens, progestins

5.15 Secretions of the Anterior Pituitary Hormones produced in the anterior pituitary include tropic hormones, which control endocrine glands and directly affect other structures, such as bones.

TROPIC HORMONES OF THE ANTERIOR PITUITARY The anterior pituitary gland secretes six main tropic hormones (**Figure 5.15**; see also Table 5.2). Two of these regulate the function of the adrenal cortex and the thyroid gland:

1. **Adrenocorticotropic hormone** (**ACTH**) controls the production and release of hormones of the adrenal cortex. The adrenal cortex, in turn, releases steroid hormones. The levels of ACTH and adrenal steroids show a marked daily rhythm (see Chapter 14).
2. **Thyroid-stimulating hormone** (**TSH**) increases the release of thyroid hormones from the thyroid gland and markedly affects thyroid gland size.

Two other tropic hormones of the anterior pituitary influence the gonads, and consequently are termed **gonadotropins**:

3. **Follicle-stimulating hormone** (**FSH**) gets its name from its actions in the ovary, where it stimulates the growth and maturation of egg-containing **follicles** and the secretion of estrogens from the follicles. In males, FSH governs sperm production.
4. **Luteinizing hormone** (**LH**) stimulates the follicles of the ovary to rupture, release their eggs, and form into structures called **corpora lutea** (singular **corpus luteum**) that secrete the sex steroid hormone progesterone. In males, LH stimulates the testes to produce testosterone. We will discuss the gonadal steroid hormones in more detail shortly.

adrenocorticotropic hormone (ACTH) A tropic hormone secreted by the anterior pituitary gland that controls the production and release of hormones of the adrenal cortex.

thyroid-stimulating hormone (TSH) A tropic hormone, released by the anterior pituitary gland, that signals the thyroid gland to secrete its hormones.

gonadotropin An anterior pituitary hormone that selectively stimulates the cells of the gonads to produce sex steroids and gametes.

follicle-stimulating hormone (FSH) A gonadotropin, named for its actions on ovarian follicles.

follicles Ovarian structures containing immature ova.

luteinizing hormone (LH) A gonadotropin, named for its stimulatory effects on the ovarian corpora lutea.

corpora lutea The structures formed from collapsed ovarian follicles subsequent to ovulation. The corpora lutea are a major source of progesterone.

The two remaining tropic hormones control milk production and body growth:

5. **Prolactin** is so named because it stimulates lactation in female mammals. But prolactin has a number of roles in addition to its actions on breast tissue. For example, it is closely involved in the parental behavior of a wide variety of vertebrate species.
6. **Growth hormone** (**GH**; also known as *somatotropin* or *somatotropic hormone*) acts throughout the body to influence the growth of cells and tissues by affecting protein metabolism. GH is released almost exclusively during sleep. Other factors also affect GH secretion. The stomach secretes a hormone, called *ghrelin* (from the proto-Indo-European root for "grow"), that evokes GH release from the anterior pituitary (Kojima et al., 1999). Ghrelin is discussed in more detail in Chapter 13. Starvation, vigorous exercise, and intense stress can all profoundly inhibit GH release (**Box 5.2**).

Now let's consider three of the organ systems stimulated by tropic hormones of the anterior pituitary: the adrenal gland, the thyroid gland, and the gonads. Each of these glands secretes hormones of its own in response to the pituitary tropic hormones.

prolactin A protein hormone, produced by the anterior pituitary, that promotes mammary development for lactation in female mammals.

growth hormone (GH) Also called *somatotropin* or *somatotropic hormone*. A tropic hormone, secreted by the anterior pituitary, that influences the growth of cells and tissues.

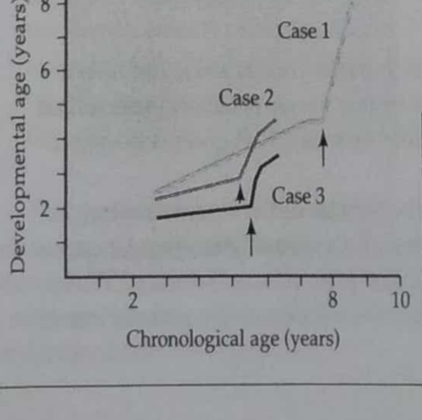
BOX 5.2 Stress and Growth: Psychosocial Dwarfism

Genie had a horrifically deprived childhood. For over 10 years, starting from the age of 20 months, she was isolated in a small, closed room, and much of the time she was tied to a potty chair. Her disturbed parents provided food, but nobody held Genie or spoke to her. When she was released from her confinement and observed by researchers at the age of 13, her size made her appear only 6 or 7 years old (Rymer, 1993).

Other less horrendous forms of family deprivation also result in failure of growth. This syndrome is referred to as **psychosocial dwarfism** to emphasize that the growth failure arises from psychological and social factors mediated through the CNS and its control over endocrine functions (W. H. Green et al., 1984). When children suffering from psychosocial dwarfism are removed from stressful circumstances, many begin to grow rapidly. The growth rates of three such children, before and after periods of emotional deprivation, are shown in the figure (arrows indicate when each child was removed from the abusive situation). These children seem to have compensated for much of the growth deficit that occurred during prolonged stress periods.

How do stress and emotional deprivation impair growth? Growth impairments appear to be mediated by changed outputs of several hormones, including growth hormone (GH), cortisol, and other hormones, known as **somatomedins** (which are normally released by the liver in response to GH). GH and the somatomedins normally stimulate cell growth; high levels of cortisol inhibit growth.

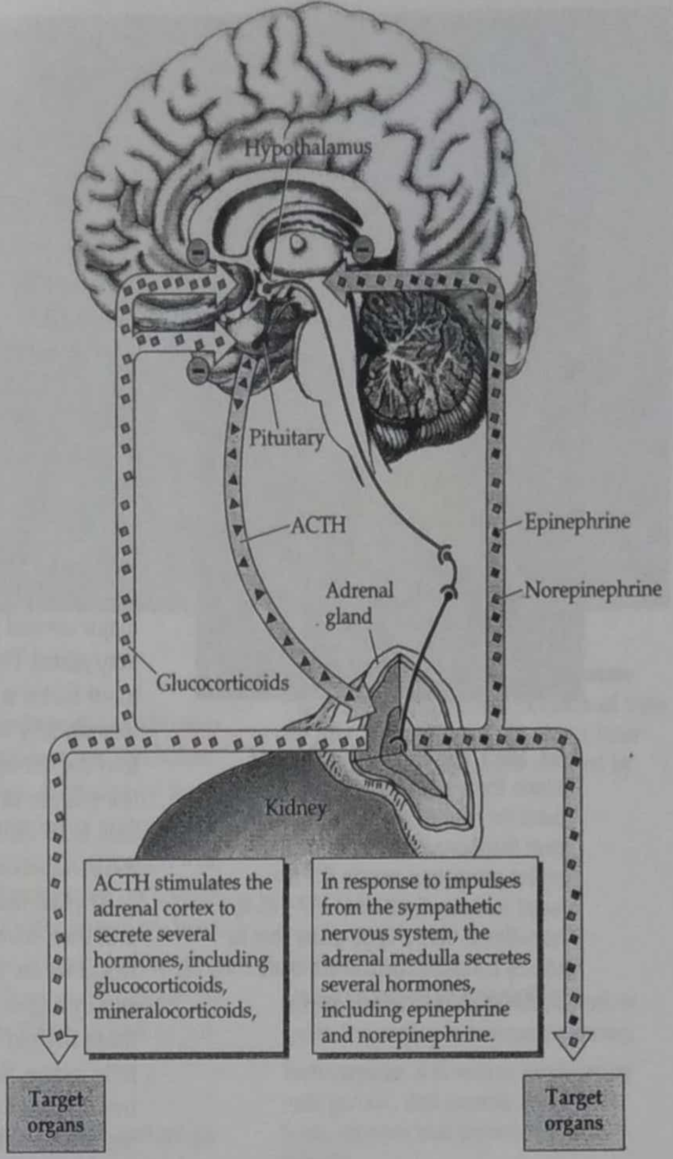
Some children with psychosocial dwarfism show almost a complete lack of release of GH, which may be caused by an absence of the releasing hormone somatocrinin from the hypothalamus (Albanese et al., 1994). Disturbed sleep has also been suggested as a cause of this failure because GH is typically released during certain stages of sleep, and children under stress show disturbed sleep patterns (L. I. Gardner, 1972). Other children who exhibit psychosocial dwarfism show normal levels of GH but low levels of somatomedins, and these hormones, along with GH, appear to be necessary for normal growth. Still other children with this condition show elevated levels of cortisol, probably as a result of stress, that inhibit growth. Some affected children show none of these hormonal disturbances, so there must also be other routes through which emotional experiences affect growth.



Growth is an example of a process that involves many factors—hormonal, metabolic, and dietary—and can therefore malfunction in a variety of ways. Cases of psychosocial dwarfism are more common than once was thought, and investigators who study this syndrome are calling for further awareness of and attention to it (W. H. Green et al., 1984). For Genie, relief came in time to restore much of her *body* growth, but her mental development remained severely limited; she has never learned to say more than a few words, and, now in her 50s, she lives in an institution.

psychosocial dwarfism Reduced stature caused by stress early in life that inhibits deep sleep.

somatomedins A group of proteins, released from the liver in response to growth hormone, that aid body growth and maintenance.


Hypothalamus
Pituitary
ACTH
Epinephrine
Norepinephrine
Adrenal gland
Glucocorticoids
Kidney
ACTH stimulates the adrenal cortex to secrete several hormones, including glucocorticoids, mineralocorticoids,
In response to impulses from the sympathetic nervous system, the adrenal medulla secretes several hormones, including epinephrine and norepinephrine.
Target organs
Target organs

5.16 Regulation of Hormones Produced by the Adrenal Glands Situated above the kidneys, each adrenal gland consists of an outer cortex (in yellow) and an inner medulla (blue). The cortex secretes glucocorticoids, mineralocorticoids, and sex steroids under the control of ACTH, which is in turn regulated by corticotropin-releasing hormone from the hypothalamus. The cells of the adrenal medulla release epinephrine and norepinephrine under the control of the sympathetic nervous system.

Two divisions of the adrenal gland produce hormones

Resting on top of each kidney is an **adrenal gland** (see Figure 5.1), which secretes a large variety of hormones (**Figure 5.16**). In mammals, the adrenal structure is divided into two major portions. The outer 80% of the gland, the **adrenal cortex**, is composed of distinct layers of cells, each producing different steroid hormones. The core 20% of the gland is the **adrenal medulla**, really a portion of the sympathetic nervous system because it is richly supplied with autonomic nerves.

The adrenal medulla releases amine hormones—**epinephrine** (or **adrenaline**) and **norepinephrine** (or **noradrenaline**)—under the control of the sympathetic nervous system. In Chapter 4 we saw that epinephrine and norepinephrine are also synaptic transmitters at certain sites in the nervous system.

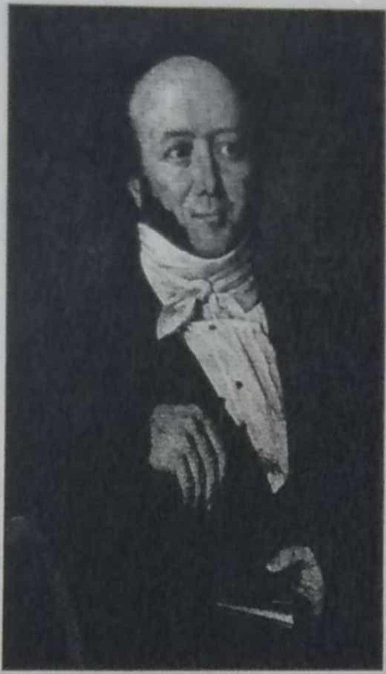
The adrenal cortex produces and secretes a variety of steroid hormones, collectively called the **adrenocorticoids** (or *adrenal steroids*). One subgroup consists of the **glucocorticoids**, so named because of their effects on the metabolism of carbohydrates, including glucose. Hormones of this type, such as **cortisol**, increase the level of blood glucose and accelerate the breakdown of proteins. In high concentrations, glucocorticoids have a marked anti-inflammatory effect; that is, they inhibit the swelling around injuries or infections. This action normally results in the temporary decrease of bodily responses to tissue injury, which is why synthetic glucocorticoids (such as prednisone) are important and useful drugs. However, sustained high levels of circulating glucocorticoids are harmful to the brain, as we'll see in Chapter 15 when we discuss stress.

A second subgroup of adrenal steroids consists of the **mineralocorticoids**, so named because of their effects on minerals such as sodium and potassium. The primary mineralocorticoid hormone is **aldosterone**, which acts on the kidneys to retain sodium and thus reduces the amount of urine produced, conserving water. This action helps maintain a homeostatic equilibrium of ions in blood and extracellular fluids (see Chapter 13).

The adrenal cortex also produces **sex steroids**, notably **androstenedione**. Androstenedione contributes to the adult pattern of body hair in men and women. In some females the adrenal cortex produces more than the normal amounts of sex hormones, causing a more masculine appearance (see Chapter 12).

The level of circulating adrenal cortical hormones is regulated in several steps (see Figure 5.16). The pituitary hormone ACTH promotes steroid synthesis in the adrenal gland. Adrenal steroids in turn exert a negative feedback effect on ACTH release. As the

adrenal gland	An endocrine gland atop the kidney.
adrenal cortex	The outer rind of the adrenal gland.
adrenal medulla	The inner core of the adrenal gland.
epinephrine or adrenaline	A compound that acts both as a hormone (secreted by the adrenal medulla under the control of the sympathetic nervous system) and as a synaptic transmitter.
norepinephrine (NE) or noradrenaline	A synaptic transmitter that is produced mainly in brainstem nuclei and in the adrenal medulla.
adrenocorticoids	Also called *adrenal steroids*. A class of steroid hormones that are secreted by the adrenal cortex.
glucocorticoids	A class of steroid hormones, released by the adrenal cortex, that affect carbohydrate metabolism and inflammation.
cortisol	A glucocorticoid stress hormone of the adrenal cortex.
mineralocorticoids	A class of steroid hormones, released by the adrenal cortex, that affect ion concentrations in body tissues.
aldosterone	A mineralocorticoid hormone, secreted by the adrenal cortex, that induces the kidneys to conserve sodium ions.
sex steroids	Steroid hormones secreted by the gonads: androgens, estrogens, and progestins.
androstenedione	The chief sex hormone secreted by the human adrenal cortex.



5.17 Isn't That a Stylish Collar? Because there is little iodine in the soil around Bern, Switzerland, vegetables grown there provide insufficient iodine even for prosperous people like the novelist Jeremias Gotthelf (1797–1854), who suffered from a large goiter that he routinely concealed behind elaborate collars. (Painting by Friedrich Dietler.)

level of adrenal cortical hormones increases, the secretion of ACTH is suppressed, so the output of hormones from the adrenal cortex diminishes. When the levels of adrenal steroids fall, the pituitary ACTH-secreting cells are released from suppression, and the concentration of ACTH in the blood rises again.

Thyroid hormones regulate growth and metabolism

Situated in the throat, just below the larynx (around the location of the Adam's apple) is the **thyroid gland** (see Figure 5.1). This gland produces and secretes several hormones. Two of these—**thyroxine** and **triiodothyronine**—are usually referred to as thyroid hormones; a third—*calcitonin*—promotes calcium deposition in bones and will not be discussed further.

The thyroid is unique among endocrine glands because it stores a large amount of hormone—at least a 100-day supply—which it slowly releases. Although thyroid hormones are amines (derived from amino acids), they behave like steroids. They bind to specialized receptors (part of the steroid receptor superfamily) found inside cells. The thyroid hormone–receptor complex then binds to DNA and regulates gene expression.

Figure 5.10 shows the control network for regulating thyroxine levels in blood. The major control is exerted by thyroid-stimulating hormone (TSH) from the anterior pituitary gland. The secretion of TSH by the pituitary is controlled by two factors. The dominant factor is the negative feedback from thyroid hormones circulating in the blood; they directly inhibit the pituitary, reducing TSH release. The second factor is the production (by the hypothalamus) of **thyrotropin-releasing hormone** (**TRH**), which stimulates the release of TSH from the pituitary. When the level of circulating thyroid hormone falls, both TRH and TSH are secreted; when TSH reaches the thyroid gland, it stimulates the production and release of thyroid hormones.

Thyroid hormones are the only substances produced by the body that contain iodine, and their manufacture is critically dependent on the supply of iodine. In parts of the world where foods contain little iodine, many people suffer from hypothyroidism. Driven by higher and higher TSH levels, the thyroid gland swells in its attempt to produce more thyroid hormones, causing a **goiter** to form. Because the soil in Switzerland has little iodine, through the nineteenth century even well-fed citizens there often had goiters (**Figure 5.17**). Today the addition of a small amount of iodine to table salt—producing *iodized salt*—ensures that we won't develop goiters even if we get insufficient iodine from our vegetables.

Remember Chuck at the start of this chapter? His problem was chronic hypothyroidism. He had been diagnosed years before and given thyroid hormone pills, but the prescription had run out and he had neglected to refill it. Six months later, when he showed up in the ER, he had not yet developed a goiter, but he was suffering. Thyroid hormones have a general effect on the nervous system, maintaining alertness and reflexes. Chuck's cognitive function became so impaired that he couldn't even remember that he had taken thyroid hormone before. But his slow knee jerk reflex suggested hypothyroidism, and blood tests confirmed that he had almost no thyroid hormone. Chuck was lucky that doctors caught his problem before he slipped into hypothyroid coma, which is fatal about 20% of the time, even when treated (Jauhar, 2003). People with less-severe hypothyroidism may appear depressed, so the hormonal imbalance is often overlooked in mild cases (C. G. Roberts and Ladenson, 2004).

Thyroid hormones also influence growth. When thyroid deficiency starts early in life, body growth is stunted and the face malformed. Thyroid deficiency also produces a marked reduction in brain size and the branching of axons and dendrites. This state, called **cretinism** or *congenital hypothyroidism*, is accompanied by mental retardation.

The gonads produce steroid hormones, regulating reproduction

Almost all aspects of reproductive behavior, including mating and parental behaviors, depend on hormones. Since Chapter 12 is devoted to reproductive behavior and physiology, at this point we will only briefly note relevant hormones and some pertinent aspects of anatomy and physiology. Female and male **gonads** (ovaries and testes, respec-

thyroid gland An endocrine gland located in the throat that regulates cellular metabolism throughout the body.

thyroxine A hormone released by the thyroid gland.

triiodothyronine A thyroid hormone.

thyrotropin-releasing hormone (TRH) A hypothalamic hormone that regulates the release of thyroid-stimulating hormone from the anterior pituitary.

goiter A swelling of the thyroid gland resulting from iodine deficiency.

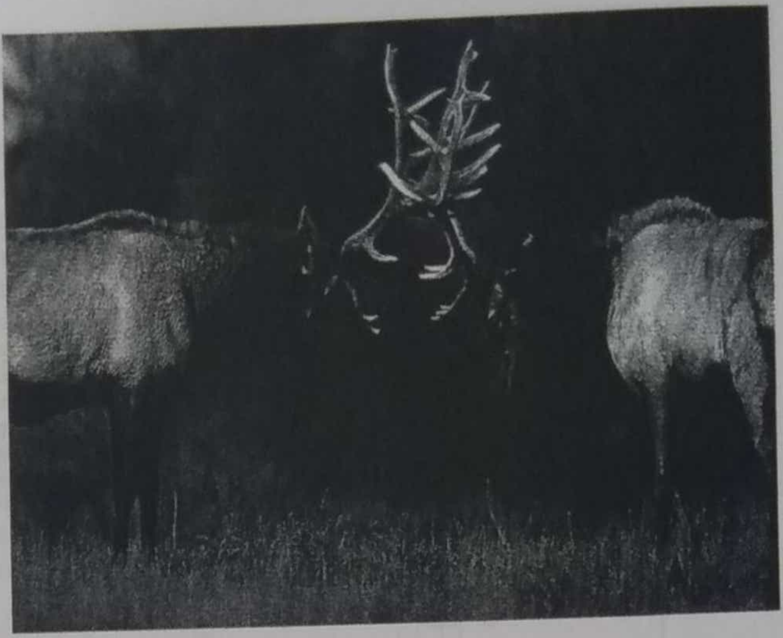
cretinism Also called *congenital hypothyroidism*. Reduced stature and mental retardation caused by thyroid deficiency during early development.

gonads The sexual organs (ovaries in females, testes in males), which produce gametes for reproduction.

tively; see Figure 5.1) consist of two different subcompartments—one to produce hormones (the sex steroids we mentioned earlier) and another to produce gametes (eggs or sperm). The gonadal hormones are critical for triggering both reproductive behavior controlled by the brain, and gamete production.

THE TESTES Within the **testes** are sperm-producing Sertoli cells and Leydig cells, which produce and secrete the sex steroid **testosterone**. Testosterone and other male hormones are called **androgens** (from the Greek *andro-*, "man," and *gennan*, "to produce"). The production and release of testosterone are regulated by LH from the anterior pituitary. LH in turn is controlled by a hypothalamic releasing hormone called **gonadotropin-releasing hormone (GnRH)**.

Testosterone controls a wide range of body changes that become visible at puberty, including changes in voice, hair growth, and genital size. In species that breed only in certain seasons of the year, testosterone has especially marked effects on appearance and behavior—for example, the antlers and fighting between males that are displayed by many species of deer (**Figure 5.18**). **Figure 5.19*a*** summarizes the regulation of testosterone secretion. As men age, testosterone levels tend to decline. Although elderly men who happen to maintain high levels of circulating testosterone perform better on tests of memory and attention than those with low levels (Yaffe et al., 2002), there have been too few studies to tell whether taking supplemental testosterone actually helps aging men (Harder, 2003; Nair et al., 2006). Furthermore, taking supplemental testosterone can sometimes increase aggressive or manic behaviors (Pope et al., 2000), as well as possibly increasing prostate cancer risk.



5.18 The Influence of a Hormone The antlers and combative behavior of male red deer, a subspecies of the North American elk, are both seasonally affected by testosterone.

THE OVARIES The paired female gonads, the **ovaries**, also produce both the mature gametes—called *ova* (singular *ovum*) or eggs—and sex steroid hormones. However, hormone secretion is more complicated in ovaries than in testes. Ovarian hormones are produced in cycles, the duration of which varies with the species. Human ovarian cycles last about 4 weeks; rat cycles last only 4 days.

The ovary produces two major classes of steroid hormones: **progestins** (from the Latin *pro*, "favoring," and *gestare*, "to bear," because these hormones help to maintain pregnancy) and **estrogens** (from the Latin *oestrus*, "gadfly" or "frenzy,"—*estrus* is the scientific term for the periodic sexual receptivity of females of many species—and the Greek *gennan*, "to produce"). Estrogens may improve aspects of cognitive functioning (Maki and Resnick, 2000), although this topic is still debated (Dohanich, 2003). Estrogens may also protect the brain from some of the effects of stress and stroke (Behl, 2002). For these reasons and others, estrogen replacement therapy has been a popular postmenopausal treatment, but evidence that these treatments increase the risk of serious diseases like cancer and heart disease has raised questions about their safety (Christensen, 1999; Turgeon et al., 2004). Many synthetic estrogens are produced and tested in search of drugs that have only the beneficial effects of the hormone, without its harmful side effects.

The most important naturally occurring estrogen is **17β-estradiol** (or just **estradiol**). The primary progestin is **progesterone**. Interestingly, estrogens make the brain sensitive to progesterone by promoting the production of progestin receptors there. Like hormone release in the testes, the ovarian release of hormones is controlled by the gonadotropins, FSH and LH. The release of these tropic hormones is controlled by GnRH from the hypothalamus (**Figure 5.19*b***). **Oral contraceptives** contain small doses of syn-

testes The male gonads, which produce sperm and androgenic steroid hormones.

testosterone A hormone, produced by male gonads, that controls a variety of bodily changes that become visible at puberty.

androgens A class of hormones that includes testosterone and other male hormones.

gonadotropin-releasing hormone (GnRH) A hypothalamic hormone that controls the release of luteinizing hormone and follicle-stimulating hormone from the pituitary.

ovaries The female gonads, which produce eggs for reproduction.

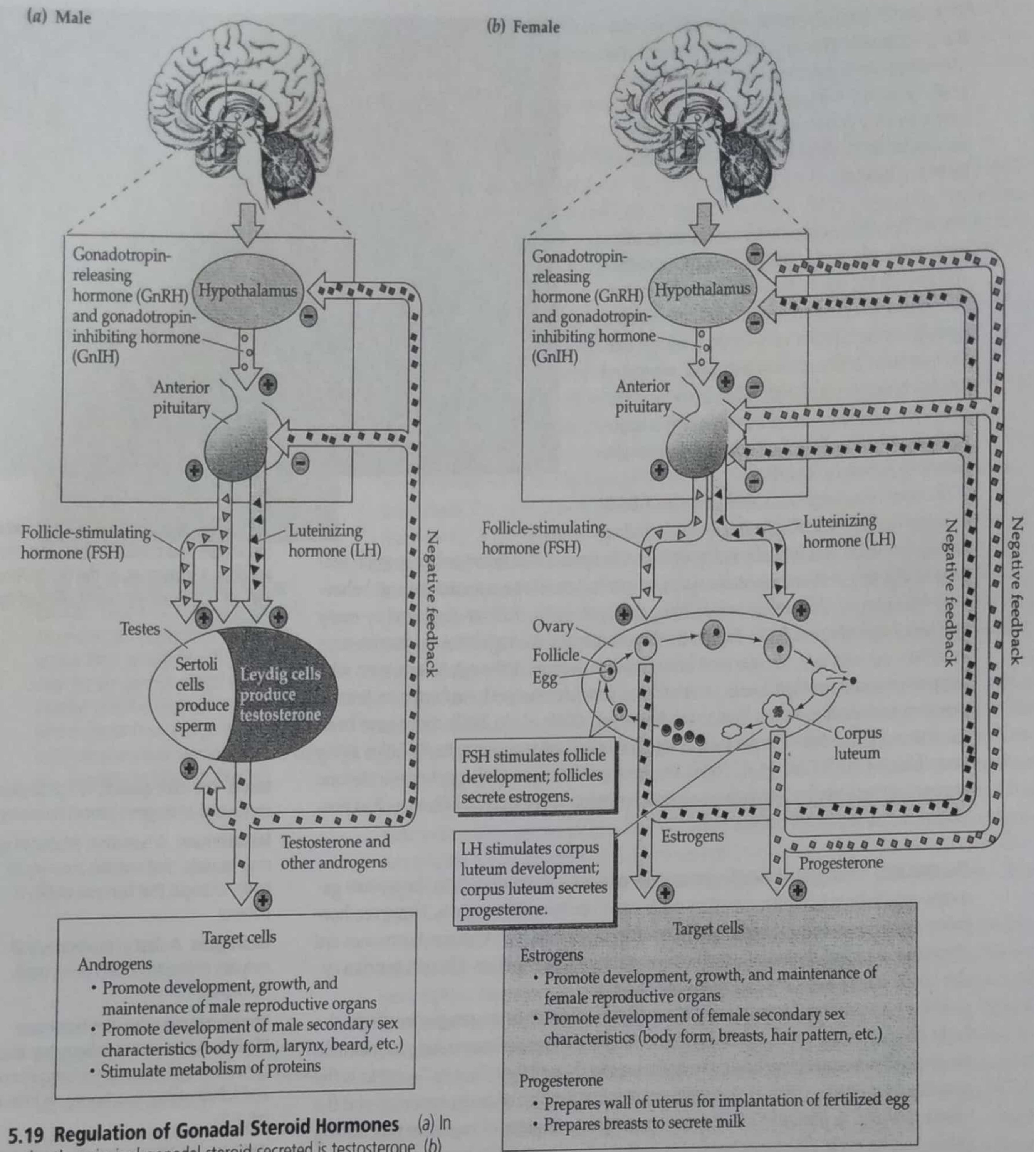
progestins A major class of steroid hormones that are produced by the ovary, including progesterone.

estrogens A class of steroid hormones produced by female gonads.

17β-estradiol or estradiol The primary type of estrogen that is secreted by the ovary.

progesterone The primary type of progestin secreted by the ovary.

oral contraceptive A birth control pill, typically consisting of steroid hormones to prevent ovulation.


(a) Male
Gonadotropin-releasing hormone (GnRH) and gonadotropin-inhibiting hormone (GnIH)
Hypothalamus
Anterior pituitary
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Negative feedback
Testes
Sertoli cells produce sperm
Leydig cells produce testosterone
Testosterone and other androgens
(b) Female
Gonadotropin-releasing hormone (GnRH) and gonadotropin-inhibiting hormone (GnIH)
Hypothalamus
Anterior pituitary
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Negative feedback
Negative feedback
Ovary
Follicle
Egg
Corpus luteum
Estrogens
Progesterone

FSH stimulates follicle development; follicles secrete estrogens.

LH stimulates corpus luteum development; corpus luteum secretes progesterone.

Target cells

Androgens
- Promote development, growth, and maintenance of male reproductive organs
- Promote development of male secondary sex characteristics (body form, larynx, beard, etc.)
- Stimulate metabolism of proteins

Target cells

Estrogens
- Promote development, growth, and maintenance of female reproductive organs
- Promote development of female secondary sex characteristics (body form, breasts, hair pattern, etc.)

Progesterone
- Prepares wall of uterus for implantation of fertilized egg
- Prepares breasts to secrete milk

5.19 Regulation of Gonadal Steroid Hormones (a) In males the principal gonadal steroid secreted is testosterone. (*b*) The female gonads produce two classes of steroids: estrogens (especially estradiol) and progestins (primarily progesterone).

thetic steroids that exert a negative feedback effect on the hypothalamus, inhibiting the release of GnRH. The lack of GnRH prevents the release of FSH and LH from the pituitary, and therefore the ovary fails to release an egg for fertilization.

Hypothalamic control of gonadotropin secretion is more complex than previously believed. Although long suspected to exist, a hypothalamic peptide that *inhibits* gonadotropins has only recently been described in birds and mammals; it has been named, sensibly, **gonadotropin-inhibiting hormone (GnIH)** (Tsutsui et al., 2006). A related peptide, **kisspeptin**, provides a stimulatory influence on GnRH secretion (J. T. Smith et al., 2006). Kisspeptin and GnIH thus work in opposition, translating inputs from the brain into controls on the gonads that have been likened to an accelerator and a brake, re-

gonadotropin-inhibiting hormone (GnIH) A hypothalamic peptide hormone that acts to reduce gonadotropin secretion by inhibiting the release of gonadotropin-releasing hormone.

kisspeptin A hypothalamic peptide hormone that acts to increase gonadotropin secretion by facilitating the release of gonadotropin-releasing hormone.

spectively (Kriegsfeld, 2006). Kisspeptin also appears to play an important role in governing the hormonal events of puberty (Han et al., 2005).

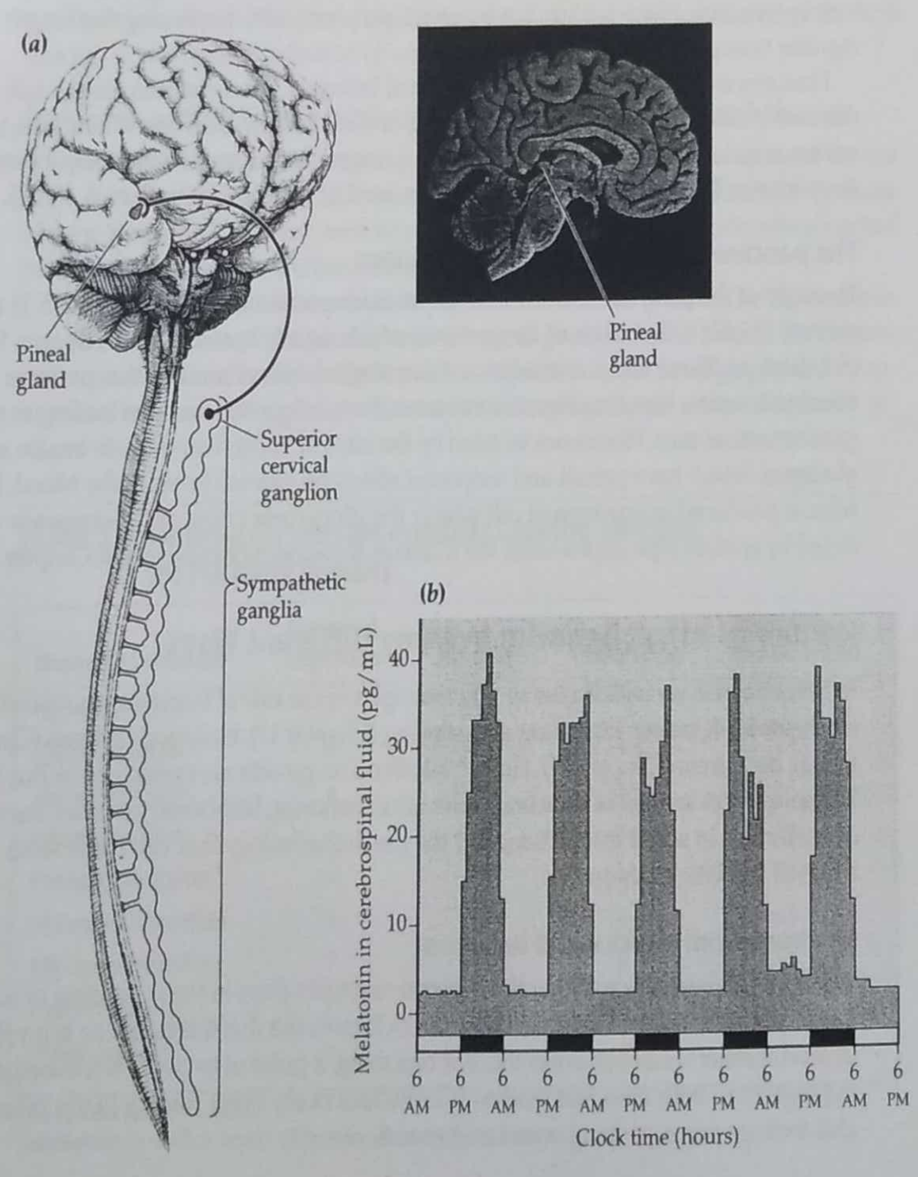
RELATIONS AMONG GONADAL HORMONES As we mentioned earlier, the steroid hormones—androgens, estrogens, progestins, and the adrenal steroids—are all based on the chemical structure of cholesterol, featuring a backbone of four interconnected carbon rings (see Figure 5.7*c*). Furthermore, progestins can be converted to androgens, and androgens in turn can be converted into estrogens. Each of these conversions is controlled by specific enzymes. The structural similarity among steroids reflects their evolutionary history: as enzymes evolved to modify old steroids, new steroids became available for signaling.

Different organs—and the two sexes—differ in the relative amounts of these hormones that they produce. For example, whereas the testis converts only a relatively small proportion of testosterone into estradiol, the ovary converts most of the testosterone it makes into estradiol. But it is important to appreciate that *no steroid is found exclusively in either males or females;* rather, the two sexes differ in the proportion of these steroids.

The pineal gland secretes melatonin

The **pineal gland** sits atop the brainstem and in mammals is overlaid by the cerebral hemispheres (**Figure 5.20*a***; see also Figure 5.1). Most brain structures are paired (with symmetrical left and right sides), but the pineal gland is a single structure. It was this unusual aspect of the pineal that led the seventeenth-century philosopher René

pineal gland A secretory gland in the brain midline; the source of melatonin release.



5.20 Regulation of the Pineal Gland (*a*) The pea-shaped pineal gland sits close to the floor of the third ventricle, atop the brainstem. Innervated by the sympathetic nervous system, specifically the superior cervical ganglion, the pineal releases melatonin. (*b*) Melatonin is released almost exclusively during the night in a wide variety of vertebrates, including humans. (After Reppert et al., 1979; photograph courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)

Descartes to propose it to be "the seat of the soul"; religious dogma of his day held that the soul, like the pineal, is indivisible.

Today we know instead that the pineal plays a crucial role in biological rhythms. Governed by the superior cervical ganglion—part of the sympathetic nervous system—the pineal releases an amine hormone called **melatonin**. The melatonin receptor is a G-coupled protein residing in cell membranes and is similar to receptors for peptide hormones. Because melatonin is released almost exclusively at night (**Figure 5.20*b***), it provides a signal that tracks day length and, by extension, the seasons.

Melatonin secretion controls breeding condition in many seasonally breeding mammals. In hamsters, for example, the lengthening nights of autumn affect activity in the superior cervical ganglion, which in turn causes the pineal to prolong its nocturnal release of melatonin. The hypothalamus responds to the prolonged exposure to melatonin by becoming extremely sensitive to the negative feedback effects of gonadal steroids. Consequently, less and less GnRH is released, resulting in less gonadotropin release, as well as atrophy of the gonads. In the spring, as days lengthen and the breeding season approaches, the melatonin signal also shortens and the process reverses: the hypothalamus becomes less sensitive to the negative feedback signal from sex steroids, the gonads grow back, and the animal becomes prepared to breed. Lesion of the pineal prevents seasonal gonadal regression, whereas chronic melatonin treatments induce regression.

In birds, light from the environment penetrates the thin skull and reaches the pineal gland directly. Photosensitive cells in the bird pineal gland monitor daily light durations. In several reptile species the pineal is close to the skull and even has an extension of photoreceptors providing a "third eye" in the back of the head. The reptile pineal photoreceptors do not form images but act as simple photocells, monitoring day length to regulate seasonal functions.

Humans are not, strictly speaking, seasonal breeders, but melatonin plays a role in our biological rhythms, especially the timing of sleep onset. Like other vertebrates, we release melatonin at night, and administering exogenous melatonin reportedly induces sleep sooner. This is why melatonin has been used to treat jet lag (Sack et al., 1992).

The pancreas secretes two main hormones

Throughout the **pancreas** (located near the stomach and duodenum; see Figure 5.1) are clusters of cells called **islets of Langerhans**, which secrete hormones directly into the bloodstream. These endocrine cells are intermingled with other cells that perform an exocrine function, secreting digestive enzymes (such as *trypsin*) into ducts leading to the gastrointestinal tract. Hormones secreted by the islets of Langerhans include **insulin** and **glucagon**, which have potent and reciprocal effects on glucose levels in the blood. Insulin is produced in one type of cell within the islets (beta cells), and glucagon is secreted by another type (alpha cells). We'll discuss these hormones further in Chapter 13.

Hormones Affect Behavior in Many Different Ways

In later chapters we will discuss specific examples of the role of hormones in reproductive behavior (Chapter 12), eating and drinking (Chapter 13), biological rhythms (Chapter 14), and stress (Chapter 15). Hormonal effects on growth are considered in Box 5.2. For now, to get an idea of how hormones affect behavior, let's briefly consider the role of hormones in social interaction, and the psychopathology that can result from too much or too little hormone.

Hormones can affect social behavior

We've already seen the role that the hormone oxytocin plays in the interaction of nursing babies and their mothers (see Figure 5.12). It turns out that this hormone is involved in several other social behaviors too. For one thing, a pulse of oxytocin is released during orgasm in both men and women (Carmichael et al., 1994), adding to the pleasurable feelings accompanying sexual encounters.

melatonin An amine hormone that is released by the pineal gland.

pancreas An endocrine gland, located near the posterior wall of the abdominal cavity, that secretes insulin and glucagon.

islets of Langerhans Clusters of cells in the pancreas that release two hormones (insulin and glucagon) with opposite effects on glucose utilization.

insulin A hormone, released by beta cells in the islets of Langerhans, that lowers blood glucose.

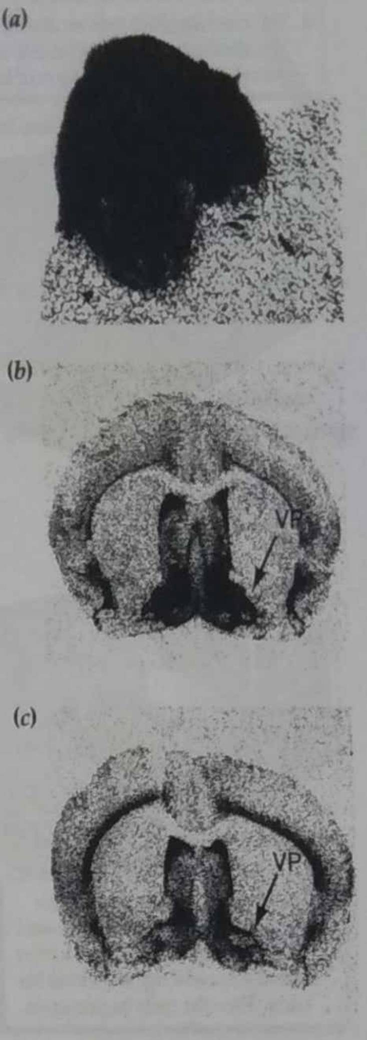
glucagon A hormone, released by alpha cells in the islets of Langerhans, that increases blood glucose.

In nonhuman animals, oxytocin and vasopressin have been shown to modulate many social processes (Lim and Young, 2006). Rodents given supplementary doses of oxytocin spend more time in physical contact with each other (Carter, 1992). Male mice with the oxytocin gene knocked out are unable to produce the hormone, and they display social amnesia: they seem unable to recognize the scent of female mice that they have met before (Ferguson et al., 2000). These oxytocin knockout males can be cured of their social amnesia with brain infusions of oxytocin, particularly in the medial amygdala (Winslow and Insel, 2002). In female mice, evidence suggests that the oxytocin released during delivery and lactation may improve the mother's ability to navigate a maze (Tomizawa et al., 2003).

In another rodent, the prairie vole (*Microtus ochrogaster*), in which couples form stable monogamous pair-bonds, oxytocin infusions in the brains of females help them bond to their mates. In male prairie voles, it is vasopressin rather than oxytocin that facilitates the formation of a preference for their female partners. In fact, the distribution of vasopressin receptors in the brains of male prairie voles may be what makes them monogamous.

Supporting this idea is the finding that, in the closely related meadow voles (*M. pennsylvanicus*), which do not form pair-bonds and have multiple mating partners, the males have far fewer vasopressin receptors in certain brain regions than do prairie voles (**Figure 5.21**) (Lim et al., 2004). And if laboratory mice are genetically engineered to produce vasopressin receptors in their brains in the same pattern that is seen in prairie vole males, then the mice are much more interested in associating with females, almost as if they were trying to form a pair-bond.

Thus it appears that oxytocin and vasopressin regulate a range of social behaviors, and that natural selection sometimes alters the social behaviors of a species through changes in the brain distribution of receptors for these two peptides.



5.21 Vasopressin and the Monogamous Brain (*a*) Prairie voles form long-lasting pair bonds. (*b*) Monogamy in male prairie voles seems to be due to the dense concentration of vasopressin receptors in the ventral pallidum (VP). (*c*) Males of the closely related meadow vole species have fewer vasopressin receptors in the VP, which may explain why they are not monogamous. (Photographs courtesy of Miranda Lim and Larry Young.)

Endocrine pathology can produce extreme effects on human behavior

Both deficient and excessive hormone secretion are associated with a variety of human physiological, anatomical, and behavioral disorders (Erhardt and Goldman, 1992). Some of these disorders have long been known, especially those that include either marked behavioral changes or anatomical abnormalities.

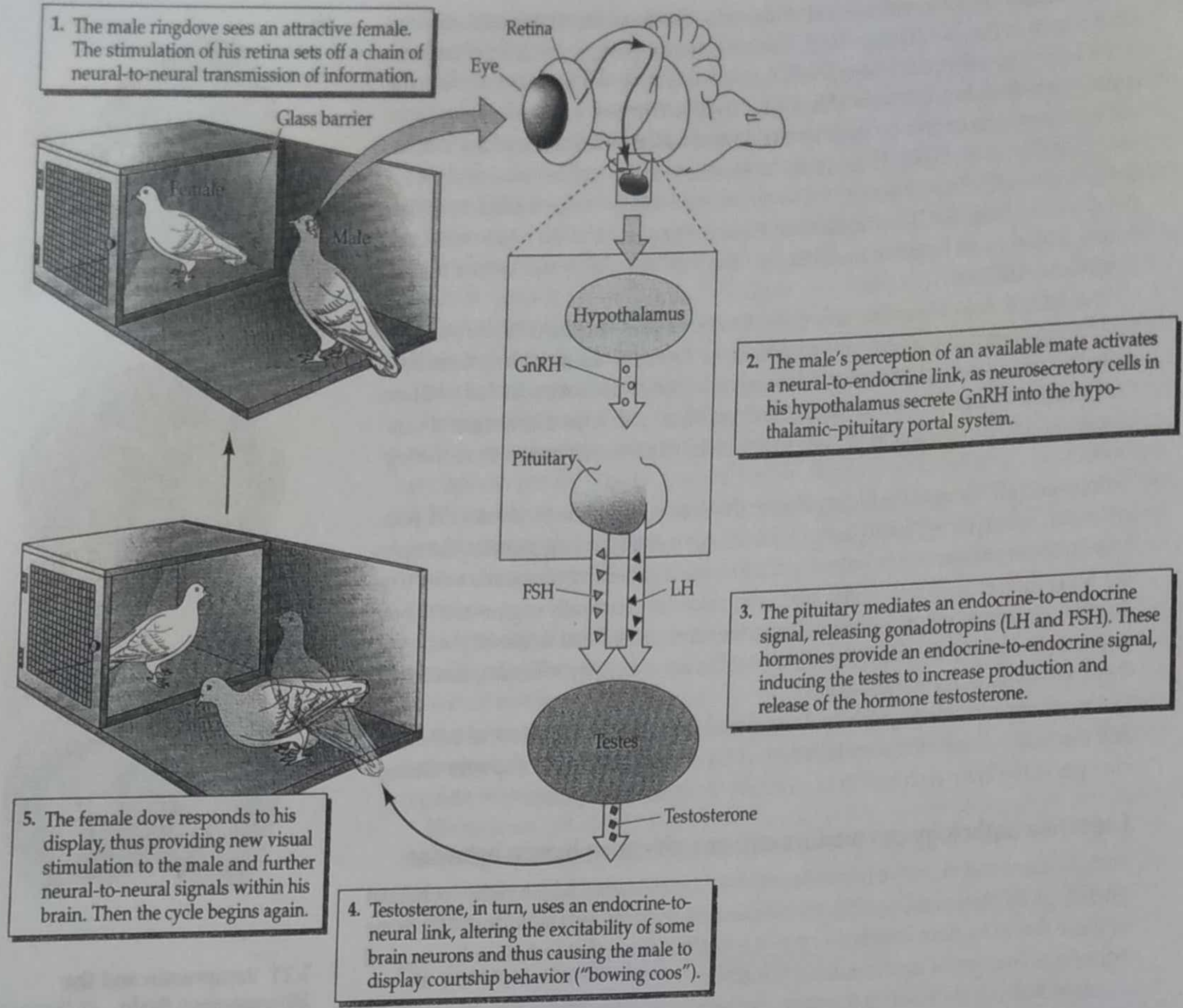
Many hormonal disorders resemble psychiatric disorders (**Table 5.3**). For example, parathyroid deficiency (the parathyroids are small glands, located behind the thyroid, that regulate calcium levels) results in calcium deposition in the basal ganglia and symptoms that resemble schizophrenia. Patients with excessive thyroid release frequently ap-

TABLE 5.3 Hormonal Disorders and Associated Cognitive, Emotional, and Psychiatric Disorders

Hormonal disorder	Impaired cognition	Anxiety	Depression	Psychosis and delirium
Hyperthyroidism	+	++	+	+
Hypothyroidism	+	+	++	++
Hypercortisolism	+	++	++	++
Hypocortisolism	—	+	++	++
Panhypopituitarism[a]	—	+	++	++
Hyperparathyroidism	+	+	++	++
Hypoparathyroidism	?	++	++	++
Hyperinsulinism	+	++	—	++
Hypoinsulinism	+	—	—	+

Note: +, sometimes; ++, often.

[a] Undersecretion of all or nearly all anterior pituitary hormones.



1. The male ringdove sees an attractive female. The stimulation of his retina sets off a chain of neural-to-neural transmission of information.

2. The male's perception of an available mate activates a neural-to-endocrine link, as neurosecretory cells in his hypothalamus secrete GnRH into the hypothalamic–pituitary portal system.

3. The pituitary mediates an endocrine-to-endocrine signal, releasing gonadotropins (LH and FSH). These hormones provide an endocrine-to-endocrine signal, inducing the testes to increase production and release of the hormone testosterone.

4. Testosterone, in turn, uses an endocrine-to-neural link, altering the excitability of some brain neurons and thus causing the male to display courtship behavior ("bowing coos").

5. The female dove responds to his display, thus providing new visual stimulation to the male and further neural-to-neural signals within his brain. Then the cycle begins again.

5.22 Four Kinds of Signals between the Nervous System and the Endocrine System

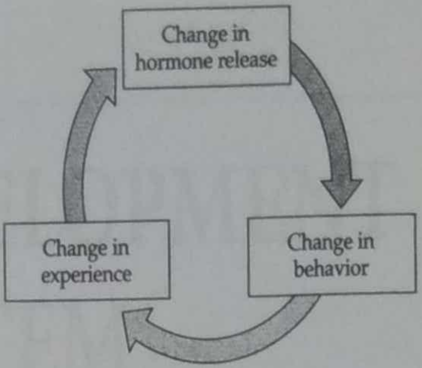
pear intensely anxious; we mentioned earlier that people like Chuck, with decreased thyroid release, may show cognitive impairments and depression. An inherited form of attention deficit hyperactivity disorder in children involves decreased sensitivity to thyroid hormone (P. Hauser et al., 1993).

A long-term excess of glucocorticoids results in **Cushing's syndrome**, a constellation of symptoms that includes fatigue, depression, *hirsutism* (unusual hair growth, such as beard growth in women), and various autonomic changes. The affective changes, especially depression, frequently long precede other physiological effects of excessive cortisol secretion. Psychiatric symptoms including psychosis have been reported by people, such as athletes, who take doses of exogenous glucocorticoids for sustained periods of time. Excessive glucocorticoid exposure is also associated with *steroid dementia syndrome*, a long-lasting impairment of cognition featuring problems with memory and attention (Wolkowitz et al., 2004).

Hormonal and Neural Systems Interact to Produce Integrated Responses

In many ways, the endocrine system and the nervous system can be viewed simply as divisions of a single master control mechanism. The two divisions work together, in an intimate and reciprocal manner, to seamlessly integrate the systems of the body, and produce adaptive responses to environmental challenges.

Cushing's syndrome A condition in which levels of adrenal glucocorticoids are abnormally high.



5.23 The Reciprocal Relations between Hormones and Behavior

Incoming environmental stimuli elicit activity in sensory pathways that project to a wide variety of brain regions, including the cerebral cortex, cerebellum, and hypothalamus. Our own behavioral responses to environmental circumstances bring further changes in stimulation. For example, if we approach an object or a sound source, we cause the visual image to become larger or the sound to become louder. Meanwhile the endocrine system is tuning our response characteristics to be consistent with the nature of the stimulus object. If the stimulus calls for action—that faint buzzing sound turns out to be coming from a nest of angry wasps, for example—energy is mobilized through hormonal routes to prepare for appropriate behaviors (namely, sprinting and swatting and maybe yelling). The behaviors themselves are, of course, executed under the control of the nervous system. Sensory receptor organs are also subject to continual adjustment, thus modifying further processing of stimuli. Another example of neural and hormonal coordination is the milk letdown reflex (see Figure 5.12).

Four kinds of signals are possible between neurons and endocrine cells: neural-to-neural, neural-to-endocrine, endocrine-to-endocrine, and endocrine-to-neural. All four kinds of signals can be found in the courtship behavior of the ringdove (**Figure 5.22**). The visual processing that occurs when a male dove sees an attractive female involves neural-to-neural transmission (step 1 in the figure). The details of the particular visual stimulus—namely, that it involves an opportunity for reproduction—activates a neural-to-endocrine link (step 2), which causes neurosecretory cells in the male's hypothalamus to secrete GnRH. The GnRH provides an endocrine-to-endocrine signal (step 3), stimulating the pituitary to release gonadotropins to induce the testes to release more testosterone. Testosterone, in turn, alters the excitability of neurons in the male's brain through an endocrine-to-neural link (step 4) and thus causes the male to display courtship behavior. The female dove responds to this display (step 5), thus providing new visual stimulation to the male, triggering another cycle of signaling within him.

The circle schema in **Figure 5.23** depicts the cyclical interactions between endocrine activity and behavior. We saw earlier how Chuck's lack of thyroid hormone drastically affected his behavior, and therefore what he experienced (i.e., not much except television). The level of circulating hormones can also be altered by experience, which in turn can affect future behavior and future experience. For example, starting to exercise or stepping out in the cold increases the level of thyroxine in the circulation. Men rooting for a sports team will produce more testosterone if their team wins (Bernhardt et al., 1998). Physical stresses, pain, and unpleasant emotional situations decrease thyroid output and trigger the release of adrenal glucocorticoids (see Chapter 15).

Conversely, each of these hormonal events will affect the brain, shaping behavior, which will once more affect the person's future hormone production. Any thorough understanding of the relationship between hormones and behavior must come to grips with these reciprocal interactions. In Chapter 15 we will learn that the neural and endocrine systems also interact extensively with the immune system.

Summary

1. Hormones are chemical compounds that act as signals in the body. They are secreted by endocrine glands into the bloodstream and are taken up by receptor molecules in target cells.
2. Neural communication differs from hormonal communication in that neural signals travel rapidly over fixed pathways, whereas hormonal signals spread more slowly and throughout the body.
3. Neural and hormonal communication systems have several characteristics in common: Both utilize chemical messages; some substances act as a hormone in some locations and as a synaptic transmitter in others. Both systems manufacture, store, and release chemical messengers. Both use specific receptors and may employ second messengers.
4. Some hormones have receptors in a wide variety of cells and can therefore influence the activity of most cells in the body. Others have receptors in only certain special cells or organs.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

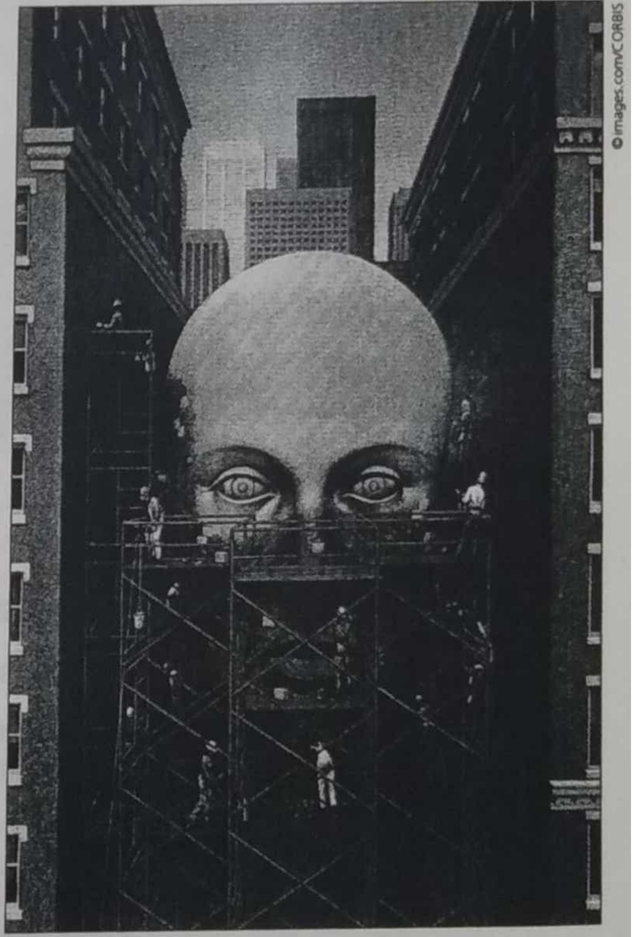
PART II

EVOLUTION AND DEVELOPMENT OF THE NERVOUS SYSTEM

Part II presents two viewpoints and two timescales for the development of the nervous system and behavior. Chapter 6 considers the *evolution* of the brain and behavior over millions of years. Chapter 7 takes up the growth of the *individual* over the months and years of the life span. Both viewpoints help us understand development, somewhat as an architect and a contractor make different but essential contributions to building a house.

The architect brings to the construction of houses the sort of perspective that evolution brings to the construction of animals. The information in the architect's plan is analogous to the information in the genome. In preparing plans, the architect calls on a long history of hard-won knowledge about structures that meet basic human needs. Using the architect's plans to construct a particular house by translating the abstract information of the blueprints into a practical, working structure, the contractor has a perspective more like that of the developing individual. The contractor's judgment and interpretation are necessary, so two houses built by different contractors from the same blueprint will not be identical, just as identical twins differ slightly.

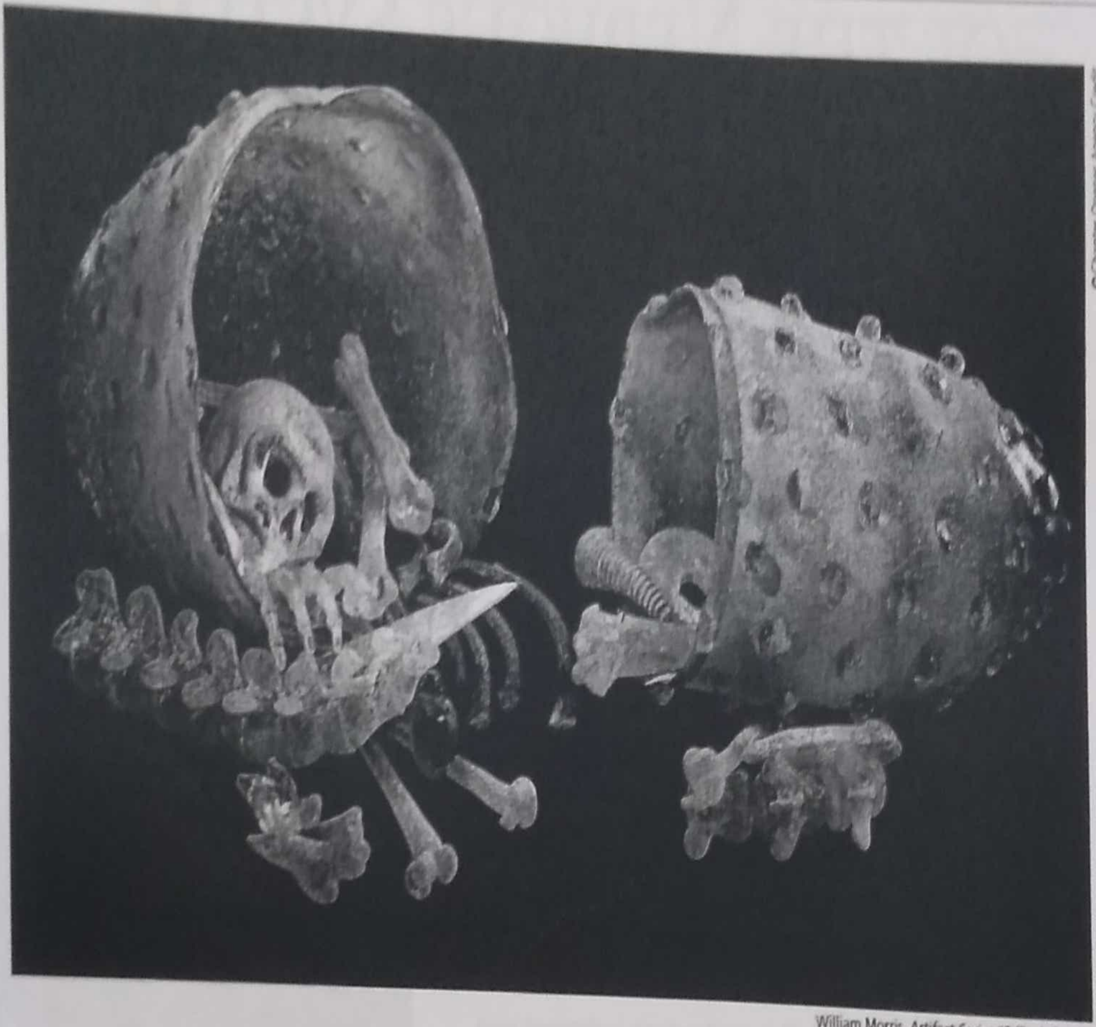
The architect tries to foresee some of the problems of construction and to build safety factors into the plans, so that small deviations or errors will not seriously impair the safety or utility of the building. But the architect also relies on the contractor to fill in details and to improvise when external conditions require it. So, too, does evolutionary wisdom, distilled in the genome, rely on the environment and experience to guide the construction of the developing brain.



© images.com/CORBIS

John Martin, *Head Being Built Between Buildings*

CHAPTER 6



© Chapter Opener Agency Credit

William Morris, *Artifact Series #9 (Burial)*, 1989

CONTENTS

Why Should We Study Other Species? 151

How Closely Related Are Two Species? 152

Comparative Methods Help Us Study the Biological Mechanisms of Behavior 158

Nervous Systems Differ Widely in Structure 159

The Evolution of Vertebrate Brains Can Be Related to Changes in Behavior 165

Evolution Continues Today 176

Evolution of the Brain and Behavior

We Are Not So Different, Are We?

If you have spent any length of time at the primate enclosure at the zoo, or watched a documentary about chimpanzees, you won't be surprised to learn that our closest animal relatives are the chimpanzees. After all, so many of their expressions and behaviors seem oddly, well, human. But despite the apparent similarities, humans and chimps are also strikingly dissimilar in many fundamental ways. Whereas humans have complex languages, chimps make only a small variety of vocal sounds. And whereas humans walk erect and have long legs, chimps locomote mostly on all fours and have relatively long arms. The human brain is about twice the size of the chimp's. Humans have spread wide from their origins in Africa, populating (or overpopulating) the globe, but chimps have remained in Africa, their numbers now dwindling at an alarming rate.

Given the many differences between humans and chimps, you might be surprised to learn that genetic material differs by only about 1.2% between the two species. One prominent scientist recently suggested that, since the genes of chimps and humans differ so little, the social context provided during the rearing of human children must be what causes them to come out so differently from chimpanzees. If that suggestion strikes you as unlikely, you are probably right. Several people have tried to rear chimpanzees like human children (see Chapter 19), and none of the chimps ever won a spelling bee or got a driver's license (not even a learner's permit).

Of course, social rearing is crucial for human development, but it cannot explain the vast differences between chimps and humans. So the problem remains: If human and chimp DNA is nearly 99% identical, how can we explain the striking differences in behavior, anatomy, and neurobiology? In other words, what makes humans human? Progress in neurobiological research is suggesting answers to this puzzle, as we will see.

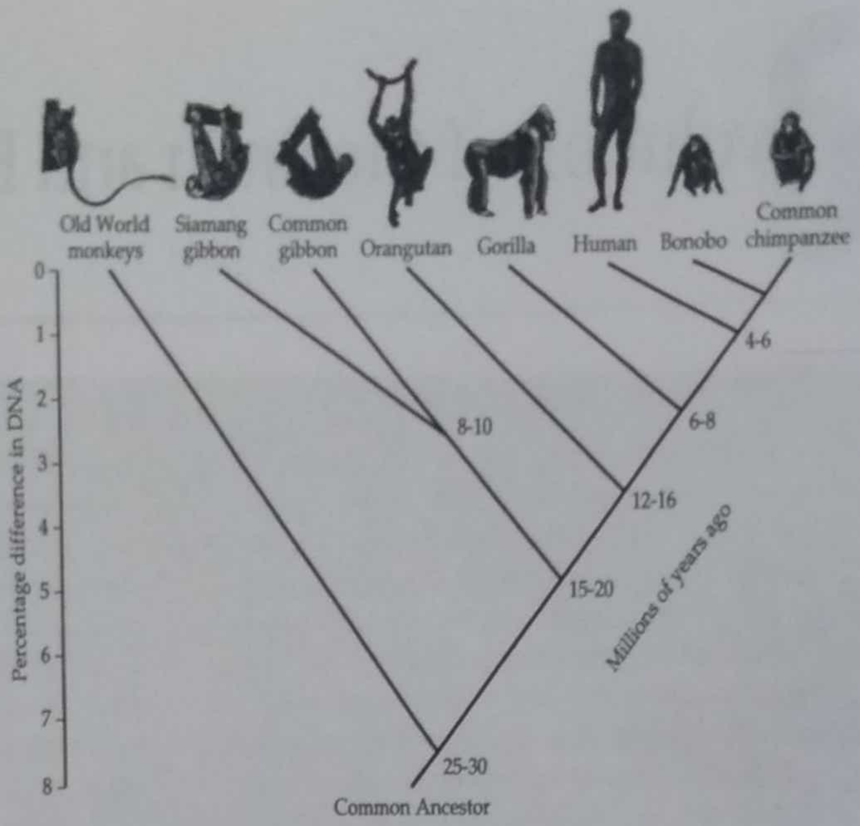
Our major objective in this chapter is to explore the intriguing story of how brains and behavior have evolved. We also consider why brain size in primates, especially in humans, increased so rapidly in our recent evolution. The quest to understand the nervous system has led to the study of a wide variety of animals, both vertebrates and invertebrates. But describing the relationships between the nervous system and behavior in even a small fraction of Earth's inhabitants would be an awesome (and dull) task unless we had a rationale beyond mere completeness. If we choose the right species to compare, however, we can learn a good deal about the principles of nervous system organization.

Why Should We Study Other Species?

One old-fashioned reason for comparing species was human-centered, based on the question, Why does the human being end up at the top of the animal order? This human-centered perspective was properly criticized because it implicitly pictured other animals as incomplete "little humans"—a view that no modern scientists see as valid. It also embraced the old idea that animals vary along a single scale from simple to complex, whereas scientists now see animal evolution as a multibranching set of radiations. Today we use comparisons of different species to gather clues about evolutionary history.

A **phylogeny** (from the Greek *phylon*, "tribe" or "kind," and *genes*, "born") is the evolutionary history of a particular group of organisms; it is often represented as a *family tree* that shows which species may have given rise to others. (Some scientists prefer to

phylogeny The evolutionary history of a particular group of organisms.



6.1 Family Tree of Apes and Humans This tree was derived from measurements of differences between pairs of species in samples of their genetic material, molecules of deoxyribonucleic acid (DNA). To see how different two species are in their genetic endowments, trace the lines from the two members of a pair to the point that connects them, and match the point with the scale on the left. For example, the line from humans and the line from chimpanzees converge at a point indicating that human DNA differs from chimpanzee DNA by only about 1.6%. The DNA of humans and of chimpanzees, in turn, differs from that of the gorilla by about 2.3%. The scale on the right gives the estimated amount of time, in millions of years, since any pair of species shared a common ancestor. For example, humans and chimpanzees diverged from a common ancestor about 4 million to 6 million years ago. (After Wildman et al., 2003.)

say *bush* rather than *tree* because the phylogeny branches so extensively.) Comparisons among extant animals, coupled with fragmentary but illuminating data from fossils, allow us to hypothesize about the history of the body and brain, and the forces that shaped them (Pennisi, 2003).

Figure 6.1 shows a recent attempt by Wildman et al. (2003) to reconstruct the family tree of apes and humans. Their diagram depicts humans and chimpanzees as more closely related to each other than either one is to the gorilla. We will say more about phylogenies a little later in the chapter.

No animal is simply sitting around providing researchers with the details of human biological history; rather, each species is busily evolving adaptations to survive in its present environment. Species with varying biological histories show different solutions to the challenges of survival and reproduction. In many cases, these pressures to adapt have led to changes in brain structure. One important adaptation is the ability to learn in order to successfully predict how to find food and to avoid danger. This capability must have arisen early in evolution, because even simple animals show lasting changes in behavior following important experiences. Understanding how the nervous systems of these simpler animals form and store memories provides insights into the mechanisms of memory in more-complex animals, including human beings, as we will see in Chapter 18.

How Closely Related Are Two Species?

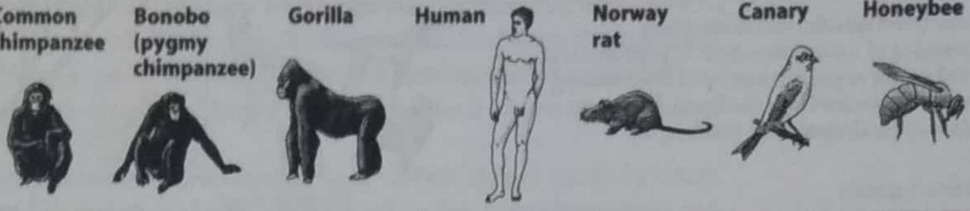
The attempt to construct the tree of life raises the question, How can we find out how closely related two species are? Some basic knowledge of this topic is important for the examples that we consider later in this chapter and in other chapters.

Early views of classification and evolution

People have probably always classified the animals around them and realized that some forms resemble each other more closely than others. The Swedish biologist Carolus Linnaeus (1707–1778) proposed the basic system that we use today. In Linnaeus's system, each species is assigned two names—the first name identifying the **genus** (plural *gen-*

genus A group of species that resemble each other because of shared inheritance.

TABLE 6.1 Classification of Some Animal Species



Taxonomic category	Common chimpanzee	Bonobo (pygmy chimpanzee)	Gorilla	Human	Norway rat	Canary	Honeybee
Kingdom	Animalia						
Phylum	Chordata						Arthropoda
Class	Mammalia					Aves	Insecta
Order	Primates				Rodentia	Passeriformes	Hymenoptera
Family	Pongidae			Hominidae	Muridae	Fringillidae	Apidae
Genus	*Pan*		*Gorilla*	*Homo*	*Rattus*	*Serinus*	*Apis*
Species	*Pan troglodytes*	*Pan paniscus*	*Gorilla gorilla*	*Homo sapiens*	*Rattus norvegicus*	*Serinus canarius*	*Apis mellifera*

era), the second name indicating the **species**. Both names are always italicized, and the genus name is capitalized. According to this system, the modern human species is *Homo sapiens*. **Table 6.1** shows the classifications of some other species.

The different levels of classification in Table 6.1 are illustrated and defined in **Figure 6.2**. The main trunk, the animal kingdom, includes all animal species. As branches divide and subdivide toward the outer reaches of the tree, each successive category includes fewer species, and the species are more closely related. The order of categories, from most broad to most narrow, is this: kingdom, phylum, class, order, family, genus, species. (Here's an aid to remembering the succession of classifications from broadest to most specific: *k*indly *p*ut *c*lothes *o*n, *f*or *g*oodness' *s*ake.) Linnaeus classified animals mainly on the basis of gross anatomical similarities and differences; he did not mean to imply anything about evolution or common ancestry.

Until about 200 years ago, it was generally believed that each species had been created separately. Then, at about the time of Linnaeus, some **naturalists**—students of animal life and structure—began to have doubts. For example, some naturalists observed that the limb bones of all mammals, no matter what the animal's way of life, are remarkably similar in many details. If these species had been specifically created for different ways of locomotion, the naturalists reasoned, they should have been built on different plans rather than all being modifications of a single plan.

As nineteenth-century geologists showed that Earth has been changing for millions of years, the newly discovered fossils of extinct species provided additional evidence for **evolution**—the gradual changing of one species into another. But a plausible *mechanism* for evolution was lacking.

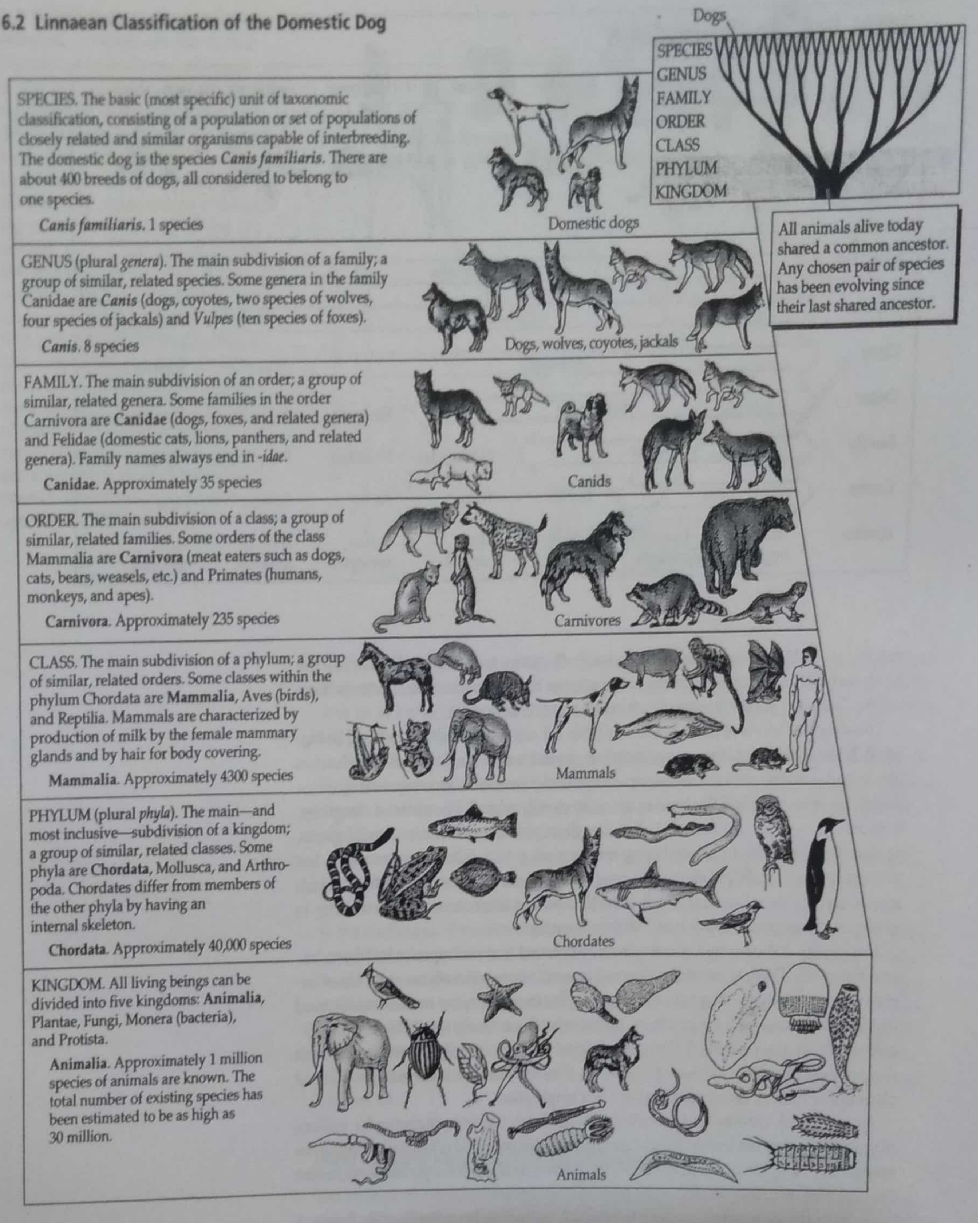
Early in the nineteenth century the French naturalist Jean-Baptiste de Lamarck (1744–1829) proposed that species evolve through the gradual accumulation of characteristics acquired by individuals throughout life as they exercise and stretch their bodies. If the ancestors to giraffes had short necks, perhaps individuals had to stretch their necks to reach leaves and this stretching caused their offspring to be born with slightly longer necks. Over generations, the necks of giraffes would become longer. But this idea, called the *inheritance of acquired characteristics*, proved to be incompatible with later discoveries about genetic inheritance.

species A group of individuals that can readily interbreed to produce fertile offspring.

naturalist A student of animal life and structure.

evolution The process by which a population of interbreeding individuals changes over long periods of time.

6.2 Linnaean Classification of the Domestic Dog



All animals alive today shared a common ancestor. Any chosen pair of species has been evolving since their last shared ancestor.

SPECIES. The basic (most specific) unit of taxonomic classification, consisting of a population or set of populations of closely related and similar organisms capable of interbreeding. The domestic dog is the species *Canis familiaris*. There are about 400 breeds of dogs, all considered to belong to one species.

Canis familiaris. 1 species

GENUS (plural *genera*). The main subdivision of a family; a group of similar, related species. Some genera in the family Canidae are ***Canis*** (dogs, coyotes, two species of wolves, four species of jackals) and *Vulpes* (ten species of foxes).

Canis. 8 species

FAMILY. The main subdivision of an order; a group of similar, related genera. Some families in the order Carnivora are **Canidae** (dogs, foxes, and related genera) and Felidae (domestic cats, lions, panthers, and related genera). Family names always end in *-idae*.

Canidae. Approximately 35 species

ORDER. The main subdivision of a class; a group of similar, related families. Some orders of the class Mammalia are **Carnivora** (meat eaters such as dogs, cats, bears, weasels, etc.) and Primates (humans, monkeys, and apes).

Carnivora. Approximately 235 species

CLASS. The main subdivision of a phylum; a group of similar, related orders. Some classes within the phylum Chordata are **Mammalia**, Aves (birds), and Reptilia. Mammals are characterized by production of milk by the female mammary glands and by hair for body covering.

Mammalia. Approximately 4300 species

PHYLUM (plural *phyla*). The main—and most inclusive—subdivision of a kingdom; a group of similar, related classes. Some phyla are **Chordata**, Mollusca, and Arthropoda. Chordates differ from members of the other phyla by having an internal skeleton.

Chordata. Approximately 40,000 species

KINGDOM. All living beings can be divided into five kingdoms: **Animalia**, Plantae, Fungi, Monera (bacteria), and Protista.

Animalia. Approximately 1 million species of animals are known. The total number of existing species has been estimated to be as high as 30 million.

Half a century after Lamarck, in 1858, Charles Darwin (1809–1892) and Alfred Russel Wallace (1823–1913) announced the hypothesis of **evolution by natural selection**. Darwin and Wallace had each hit upon the idea independently. Darwin had been accumulating evidence to support the hypothesis ever since, as a young naturalist in the 1830s, he had voyaged on the HMS *Beagle* to South America and the Galápagos Islands, a chain of islands on the equator far from the west coast of South America. The gov-

evolution by natural selection The Darwinian theory that evolution proceeds by differential success in reproduction.

ernor of the Galápagos had pointed out to Darwin that the giant tortoises differed in their shell patterns from island to island. Later, examining the specimens of finches that he had collected on different Galápagos islands, Darwin observed that the birds also differed from island to island. Although the birds resembled finches on the mainland, those on the Galápagos appeared to represent several different species, suited by their body sizes and beaks to obtaining different kinds of food, such as nuts or seeds or insects.

In 1859, Darwin published his revolutionary book *On the Origin of Species by Means of Natural Selection*. The hypothesis he stated was based on four main observations and one important inference. The observations were these:

1. Reproduction will tend to increase a population rapidly unless factors limit it.
2. Individuals of a given species are not identical.
3. Some of the variation among individuals is inherited.
4. Not all the offspring of a given generation survive to reproduce.

The inference was that the variations among individuals affect the probability that they will survive, reproduce, and pass on their characteristics. Thus the individuals better suited to the prevailing conditions will be those that reproduce and furnish the next generation. Over time, this selection at the level of individual organisms can yield substantial changes in the population.

The concept of evolution by natural selection has become one of the major organizing principles in all the life sciences, directing the study of behavior and its mechanisms, as well as the study of morphology (form and structure). Darwin (1859) wrote, prophetically, that because of his work, "Psychology will be based on a new foundation, that of the necessary acquirement of each mental power and capacity by gradation" (p. 113); in other words, psychological functions are as much products of evolution as are the organs of the body.

Darwin later added another evolutionary principle: **sexual selection** (1871). This principle holds that members of each sex exert selective pressures on the other in terms of both anatomical and behavioral features that favor reproductive success. Thus, for example, female choices have led to the ornamental but costly tails of peacocks. We will discuss this principle later in this chapter.

Modern evolutionary theory combines natural selection and genetics

A gap in Darwin's theory was that he could not specify the source of the variation upon which natural selection acts or the mechanism by which biological inheritance works. A major step to round out the theory of evolution was accomplished by the pioneering work of an Austrian monk and botanist named Gregor Johann Mendel (1822–1884). On the basis of his research with pea plants, Mendel published the laws of inheritance in an obscure journal in 1866 (Mendel, 1967). Not until 1900, however, was Mendel's work rediscovered and linked to evolution by the Dutch biologist Hugo de Vries (1848–1935), who was conducting experiments with primroses. De Vries went beyond Mendel in an important respect: he found that occasionally a new variety arose spontaneously and then passed its characteristics on to successive generations. In 1901, De Vries pointed out that, in such cases, evolution could occur by sudden jumps, or **mutations**, as he called these changes. (Nowadays, scientists deliberately induce mutations in plants and animals, as we will discuss in Box 7.3.) Thus De Vries discovered that evolution is not only the slow process that Darwin hypothesized; it can also occur rapidly.

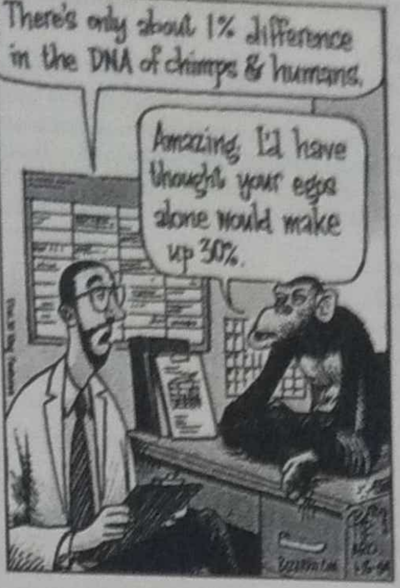
Although **genetics**, the study of the mechanisms of inheritance, started with plants such as the pea and the primrose, investigators soon began to study organisms that reproduce more rapidly. An example is the fruit fly *Drosophila*, whose generation time is 10 days and whose salivary glands produce giant chromosomes that are visible under a light microscope. **Chromosomes** (from the Greek *chroma*, "color," and *soma*, "body") are rod-shaped assemblies of DNA in the nucleus of each cell that bear genetic information. Since 1882 it had been known that chromosomes replicate themselves during cell division, but the significance of this phenomenon did not become apparent until

sexual selection Darwin's theoretical mechanism for the evolution of anatomical and behavioral differences between males and females.

mutation A change in the nucleotide sequence of a gene as a result of unfaithful replication.

genetics The study of inheritance, including the genes encoded in DNA.

chromosome A complex of condensed strands of DNA and associated protein molecules; found in the nucleus of cells.


There's only about 1% difference in the DNA of chimps & humans.
Amazing. I'd have thought your egos alone would make up 30%.

6.3 We Are Related, Aren't We?

Mendel's work was rediscovered. Many of the findings about genetic mechanisms made with *Drosophila* and even with bacteria hold true for larger organisms, such as humans, that reproduce much more slowly.

By the 1940s, scientists realized that nucleic acids are the instruments of genetic inheritance. In 1953, James D. Watson (1928–) and Francis Crick (1916–2004) announced that the structure of the DNA molecule, which forms chromosomes, is a double helix. This discovery led in turn to the cracking of the genetic code, a topic that is taken up in the appendix. Crick and Watson were awarded the Nobel Prize in Physiology or Medicine in 1962. As a key to their discovery, Watson and Crick relied on X-ray photographs of DNA taken by Rosalind Franklin (1920–1958), and some scientists believe that if she had not died prematurely, she might have shared the Nobel Prize (Maddox, 2003).

Both gradual changes within a species and the formation of new species can now be understood in the light of modern evolutionary theory, which combines Darwin's hypothesis of natural selection with modern genetics and molecular biology. Further insights continue to be added by research in these and related fields, such as developmental biology, paleontology, and systematic biology.

Newer methods aid in classifying animals and inferring evolution

The field of **taxonomy** (from the Greek *taxis*, "arrangement," and *nomos*, "law"), or *classification*, of animals is an ongoing endeavor. Taxonomists continue to be challenged as previously unknown animals are discovered, as new techniques become available, and as new concepts arise.

For example, some of the relationships among apes and humans are still being debated. You may have noticed that Figure 6.1 and Table 6.1 differ in their placement of human beings. Figure 6.1 is based mainly on comparisons between samples of DNA among species (**Figure 6.3**). It shows chimpanzees closer to humans than to gorillas in their genes. This phylogeny has led Wildman et al. (2003) to propose that the genus *Homo* be enlarged to include the chimpanzees. Table 6.1, which is based on body measurements and behavior—and on traditional thinking about the place of humans in nature—puts both chimpanzees and gorillas in the family Pongidae (the great apes), whereas humans are traditionally placed in their own family, Hominidae. Wildman and his associates point out that the small genetic divergence between humans and chimpanzees, and the fact that the two species separated apparently quite recently (sharing a common ancestor less than 6 million years ago), is within the limits for other species that are considered part of the same genus.

Both the fossil record and DNA analyses help us classify animals and make inferences about their evolution. Fossils can be used to trace the families of many living species into the remote past and to clarify some classifications. The fossil record has been invaluable, but it is still very incomplete; important fossils are being discovered every year. For example, an international group led by paleontologist Tim White discovered, in Ethiopia, the oldest *Homo sapiens* skulls (T. D. White et al., 2003). From their rock environment, these skulls were dated to about 160,000 years ago (Clark et al., 2003)—just the age that had been estimated from DNA evidence for the emergence of the first modern humans. The fossil record also reveals many extinct species, including extinct members of the hominid line. For another example of extinctions, it is estimated that, since birds first evolved about 150 million years ago, a total of about 150,000 species of birds have existed, but only about 9000 exist today (Sibley and Ahlquist, 1990).

We have already mentioned the development of molecular techniques that allow us to study genetic material and to measure genetic variation with precision. Analysis of genetic material—fragments of DNA molecules—from many species has confirmed many classifications and improved others. Furthermore, quantifying the difference between base pairs in DNA samples from two species allows investigators to estimate the genealogical distance between them. Thus, DNA analyses and comparisons help in constructing phylogenetic trees such as the one in Figure 6.1.

taxonomy The classification of organisms.

In addition, DNA appears to change at a relatively steady average rate in all lineages of a given order of animals (Hillis et al., 1996). Thus the proportion of differences between DNA samples from two species can be used as a "molecular clock" to estimate how long ago they diverged from a common ancestor. The absolute times in Figure 6.1 should be considered with caution, however, because scientists are still discussing and testing ideas about the calibration of the molecular clocks. Nonetheless, the relative time periods—the overall picture—are well agreed upon.

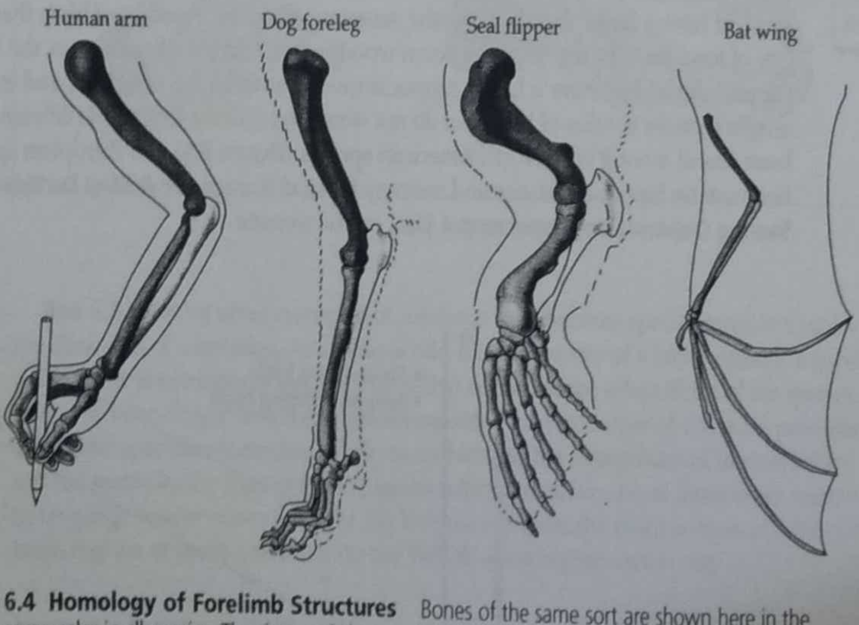
Small fragments of DNA have been obtained from insects fossilized in amber as long as 40 million years ago, helping us to discriminate among possible lines of descent of some modern insects and to test further the "clock" of changes in DNA over time (Poinar, 1994). A fictionalized version of this technique helped make millions of dollars for the writers and producers of the *Jurassic Park* movies.

Estimates from fossil and DNA evidence do not always agree completely in dating branches of the evolutionary tree. Fossil dates tend to be too recent, because we can never find the first specimen of a given species. Molecular dates have tended to be too old, because of problems with calibrating rates of change of DNA over time. But Benton and Ayala (2003) show that these discrepancies are diminishing, and most paleontological and molecular dates now agree.

Evolution may converge upon similar solutions

Adaptation to similar ecological features may bring about similarities in behavior or structure among animals that are only distantly related. These similarities are referred to as examples of **convergent evolution**. For example, the body forms of a tuna and a dolphin resemble each other because they each evolved for efficient swimming, even though the tuna is a fish and the dolphin is a mammal descended from terrestrial ancestors. Such a resemblance is an example of **homoplasy**, a resemblance between features that is due to convergent evolution.

By contrast, a **homology** is a resemblance based on common *ancestry*, such as the similarities in forelimb structures of mammals that we described earlier (**Figure 6.4**). **Analogy** refers to similar *function*, although the structures may look different (e.g., the hand of a human and the trunk of an elephant are analogous).



6.4 Homology of Forelimb Structures Bones of the same sort are shown here in the same color in all species. The sizes and shapes of the bones of the forelimb have evolved so that they are adapted to widely different functions: skilled manipulation in humans, locomotion in dogs, swimming in seals, flying in bats. The similarities among the sets of bones reflect descent from a common ancestor.

convergent evolution The evolutionary process by which responses to similar ecological features bring about similarities in behavior or structure among animals that are only distantly related (i.e., that differ in genetic heritage).

homoplasy The similar appearance of features (e.g., the body forms of a tuna and a dolphin), often due to convergent evolution.

homology A resemblance based on common ancestry.

analogy Similarity of function, although the structures of interest may look different.

Comparative Methods Help Us Study the Biological Mechanisms of Behavior

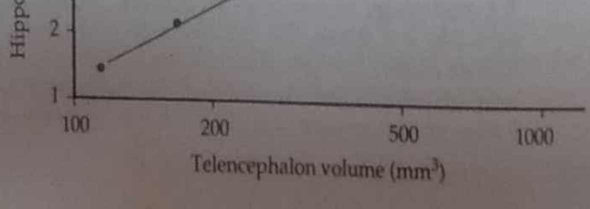
Comparing the behavior and neural mechanisms of different kinds of animals in different ecological niches is important in biological psychology. We use such comparisons in every chapter of this book. Although studying only one species may yield important information, comparing two or more carefully chosen species leads to a much deeper understanding of the phenomena because the evolutionary framework provides additional explanatory power. Let's look at a few examples.

Some ways of obtaining food require bigger brains than others

Most species of animals spend much of their time and energy in the pursuit of food, often using elaborate strategies. Researchers have found that the strategies that different species use to obtain food are correlated to brain size and structure. For example, mammals that eat food distributed in clusters that are difficult to find (such as ripe fruit) tend to have brains larger than those of related species whose food is rather uniformly distributed and easy to find (such as grass or leaves). This relationship has been found within families of rodents, insectivores (such as shrews and moles), lagomorphs (such as rabbits and pikas) (Clutton-Brock and Harvey, 1980), and primates (Mace et al., 1981).

Finding novel ways of getting food is related to the size of the forebrain in different orders of birds (Lefebvre et al., 1997). Investigators collected accounts of novel behavior from ornithological journals (e.g., magpies digging up potatoes, house sparrows searching car radiator grilles for insects, crows dropping palm nuts in the paths of cars that run over and open them). Separate data sets were prepared for North America and the British Isles. In both areas, more-innovative species have relatively larger forebrains. The results suggest selection for increased size of the forebrain to cope with environmental challenges and opportunities in new, flexible ways. Later in the chapter we will see an extension of this kind of study to species of primates, also showing that increased size of the forebrain is related to innovation (Reader and Laland, 2002).

Some behavioral adaptations have been related to differences in relative sizes of certain brain structures. For example, some species of bats find their way and locate prey by hearing; others rely almost entirely on vision. In the midbrain, the auditory center (the inferior colliculus) is much larger in bats that depend on hearing; bats that depend on sight have a larger visual center (the superior colliculus). Families of birds that store bits of food for later use (e.g., the acorn woodpecker, Clark's nutcracker, or the black-capped chickadee) have a larger hippocampus relative to the forebrain and to body weight than do families of birds that do not store food (Sherry, 1992). This difference has been found among both North American species (**Figure 6.5**) and European species. For more on hippocampal size and memory for food storage, see **A Step Further: Food Storing Depends on Hippocampal Size**, on the website.



6.5 Food Storing in Birds as Related to Hippocampal Size
Food-storing species of birds have twice as large a hippocampus in relation to their forebrain (the telencephalon) as do species that do not store food. Note that both axes on this graph are logarithmic. (After Sherry et al., 1989.)

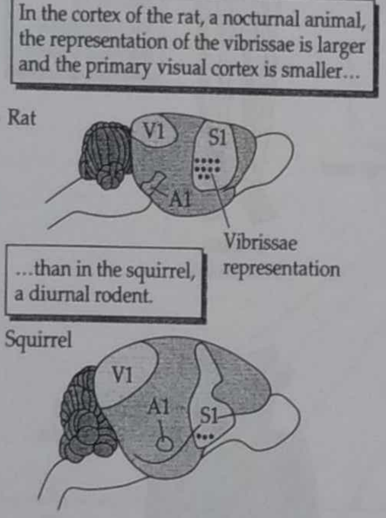
BOX 6.1 To Each Its Own Sensory World

Lifestyle differences among mammals are related to the organization of the cerebral cortex, as the examples here show. The rat (*Rattus norvegicus*) is nocturnal and uses its whiskers to find its way in the dark. About 28% of the representation of the rat's body surface in the cortex is devoted to the whiskers (vibrissae), whereas only about 9% of the body surface representation of the squirrel (*Sciurus carolinensis*) is devoted to the whiskers (see Figure A) (Huffman et al., 1999). In addition, the nocturnal rat makes rather little use of vision, and its primary visual cortex (V1) is relatively small compared with that of the squirrel, which is diurnal.

The remarkable platypus (*Ornithorhynchus anatinus*) is an egg-laying mammal that lives in and around streams in eastern Australia and Tasmania. Because of its ducklike bill and webbed feet, some scientists thought it might be a hoax when the first skin preparations were brought to Europe at the beginning of the nineteenth century. The platypus is largely nocturnal and dives into murky waters, closing its eyes, ears, and nostrils as it hunts for insects, shrimp, and crayfish. How it senses its prey remained a mystery until the 1980s, when investigators found that the main sensory organ of the platypus is its bill, which is about 7 cm long in a 160-cm-long adult.

The bill has about 16 longitudinal stripes of receptors: stripes of touch receptors alternating with touch-electrical receptors (see Figure B) (Manger et al., 1998). As the platypus moves its bill underwater, it can detect prey by both the mechanical ripples and the changes in electrical fields that they cause. In keeping with the importance of the bill in locating prey, almost all of the somatosensory cortex (S1 and S2) in the platypus is devoted to the bill (see Figure B), and the primary visual (V1) and auditory (A1) areas are small (Krubitzer et al., 1995).

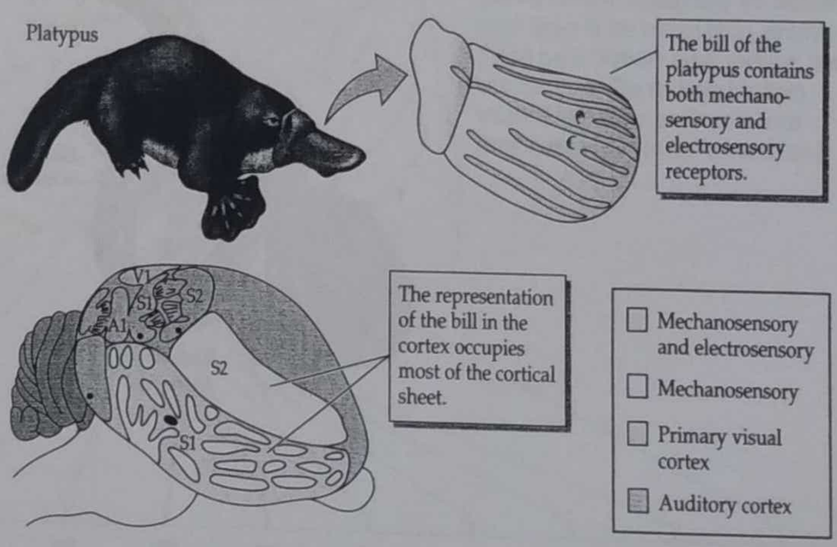
(A)



In the cortex of the rat, a nocturnal animal, the representation of the vibrissae is larger and the primary visual cortex is smaller…

…than in the squirrel, a diurnal rodent.

(B)



The bill of the platypus contains both mechanosensory and electrosensory receptors.

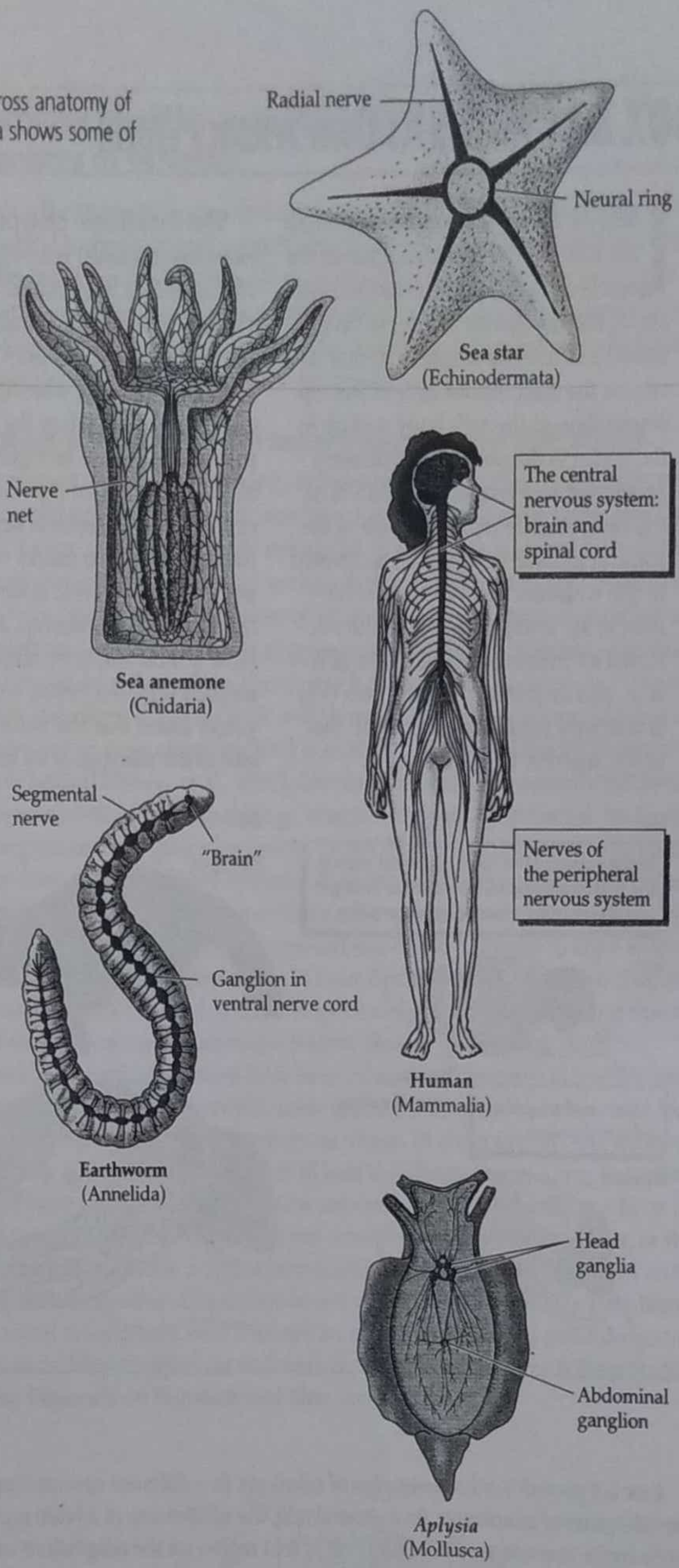
The representation of the bill in the cortex occupies most of the cortical sheet.

Box 6.1 provides other examples of solutions that different species employ to solve the dilemmas of adaptation. As a general rule, the relative size of a brain region is a good guide to the importance of the function of that region for the adaptations of the species. Our understanding of how these differences in size and structure of the brain promote behavioral specializations should help us understand the neural basis of human behavior. For example, the sizes of some regions in the human temporal lobes seem related to language function (see Chapter 19). You can compare the relative sizes of different brain regions of many mammals on the Web at www.brainmuseum.org.

Nervous Systems Differ Widely in Structure

Having compared aspects of the nervous systems of a few species, let's look more broadly at the variety of nervous systems of a few phyla of animals. **Figure 6.6** shows the gross anatomy of the nervous systems of some representative animals.

6.6 A Comparative View of Nervous Systems Gross anatomy of the nervous system in representative animals from five phyla shows some of the variety.

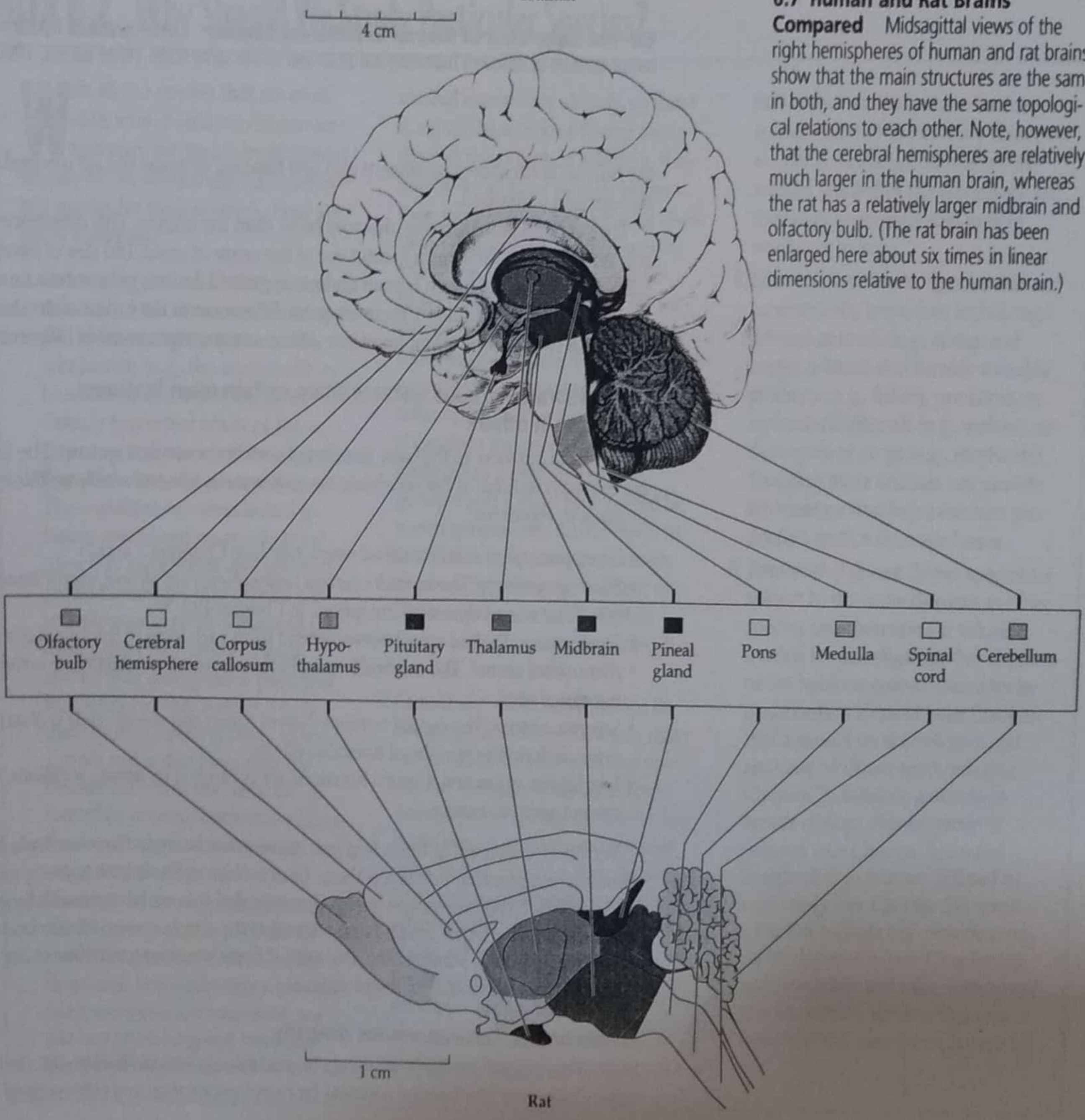

Radial nerve
Neural ring
Sea star
(Echinodermata)
Nerve net
Sea anemone
(Cnidaria)
The central nervous system: brain and spinal cord
Nerves of the peripheral nervous system
Human
(Mammalia)
Segmental nerve
"Brain"
Ganglion in ventral nerve cord
Earthworm
(Annelida)
Head ganglia
Abdominal ganglion
Aplysia
(Mollusca)

A leading researcher in comparative neurosciences, Theodore H. Bullock, asserted in 1984, "We cannot expect truly to comprehend either ourselves or how the nervous system works until we gain insight into this range of nervous systems, from nerve nets and simple ganglia in sea anemones and flatworms to the optic lobes of dragon flies, octopuses, and lizards to the cerebral cortex in primates" (p. 473). Faced with the enormous complexity of the vertebrate brain, with its billions of nerve cells, researchers have turned instead to the nervous systems of some invertebrates that have only hundreds or thousands of neurons. An exhaustive description of the "wiring diagram" of the nervous system and how it relates to behavior may someday be possible with these invertebrates. First, however, let's start our comparison with brains more similar to our own.

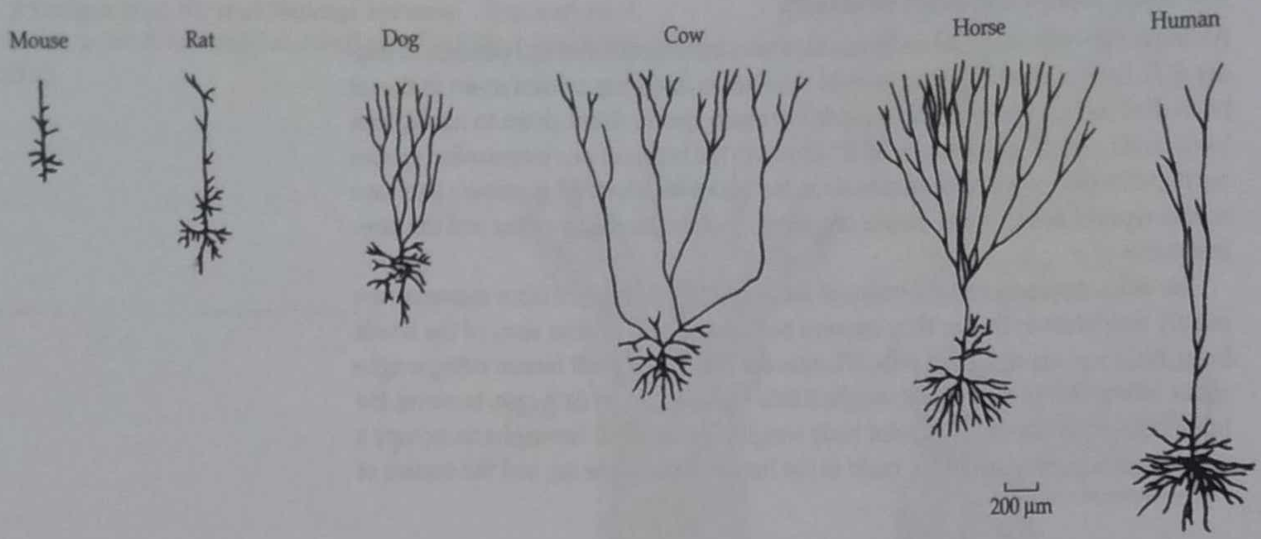
Mammals share main brain structures

A comparison of human and rat brains illustrates basic similarities and differences (**Figure 6.7**). Each of the main structures in the human brain has a counterpart in the rat brain. This comparison could be extended to much greater detail, down to nuclei, fiber tracts, and types of cells. Even small structures in the brains of one mammalian species are found to have exact correspondence in the brains of others. All mammals also have similar types of neurons and similar organization of the cerebellar cortex and the cerebral cortex.

The differences between the brains of humans and the brains of other mammals are mainly quantitative; that is, they concern both actual and relative sizes of the whole brain, brain regions, and brain cells. Whereas the brain of an adult human being weighs about 1400 g, that of an adult rat weighs a little less than 2 g. In each case, however, the brain represents about 2% of total body weight. The cerebral hemispheres occupy a much greater proportion of the brain in the human than in the rat, and the surface of



6.7 Human and Rat Brains Compared Midsagittal views of the right hemispheres of human and rat brains show that the main structures are the same in both, and they have the same topological relations to each other. Note, however, that the cerebral hemispheres are relatively much larger in the human brain, whereas the rat has a relatively larger midbrain and olfactory bulb. (The rat brain has been enlarged here about six times in linear dimensions relative to the human brain.)



6.8 The Same Kind of Neuron in Different Species These pyramidal neurons from the motor cortices of different mammals are all drawn to the same scale. (After Barasa, 1960.)

the human brain shows prominent gyri and fissures, whereas the rat cerebral cortex is smooth and unfissured.

The rat has relatively larger olfactory bulbs than the human. This difference is probably related to the rat's much greater use of the sense of smell. The size of neurons also differs significantly between human and rat; in general, human neurons are much larger than rat neurons. In addition, there are great differences in the extent of dendritic trees. **Figure 6.8** shows some examples of size differences among neurons of different species.

All vertebrate nervous systems share certain main features but differ in others

Let's extend our view to the basic features of vertebrate nervous systems. The following are the main features of the vertebrate nervous system, some of which are illustrated for humans in Figure 6.6:

- *Development from a hollow dorsal neural tube* (see Chapters 2 and 7).
- *Bilateral symmetry*. The human cerebral hemispheres are almost mirror images. (We'll see some interesting exceptions in Chapter 19.)
- *Segmentation*. Pairs of spinal nerves extend from each level of the spinal cord.
- *Hierarchical control*. The cerebral hemispheres control or modulate the activity of the spinal cord.
- *Separate systems*. The central nervous system (brain and spinal cord) is clearly separate from the peripheral nervous system.
- *Localization of function*. Certain functions are controlled by certain locations in the central nervous system.

Vertebrates have all of these features in common because they descended from a common ancestor that possessed them. Examination of the brains of many classes of the 10,000 to 20,000 vertebrate species has revealed that vertebrates with larger bodies tend to possess larger brains. No matter what the size, however, all vertebrate brains have the same major subdivisions. The main differences among vertebrates are the absolute and relative sizes of different regions.

Invertebrates show enormous diversity

Most of the animals on Earth are invertebrates, animals without backbones. (In fact, the order Coleoptera [the beetles] contains far more species than any other order!) The invertebrates far exceed vertebrates in many ways, including number, diversity of appearance, and variety of habitat. Whereas invertebrates make up 17 phyla, the vertebrates are only a part of one phylum: Chordata (the chordates). The abundance of invertebrates is clearly demonstrated by the following estimate: for each person on Earth, there are at least 1 billion insects, which are just one type of invertebrate.

Neuroscientists focus on certain invertebrates because of the relative simplicity of their nervous systems and the great varieties of behavioral adaptation that they display. Furthermore, invertebrates possess elaborate sensory systems that permit some stimuli to be detected with exquisite sensitivity. **Box 6.2** provides additional explanations for why we should study particular species.

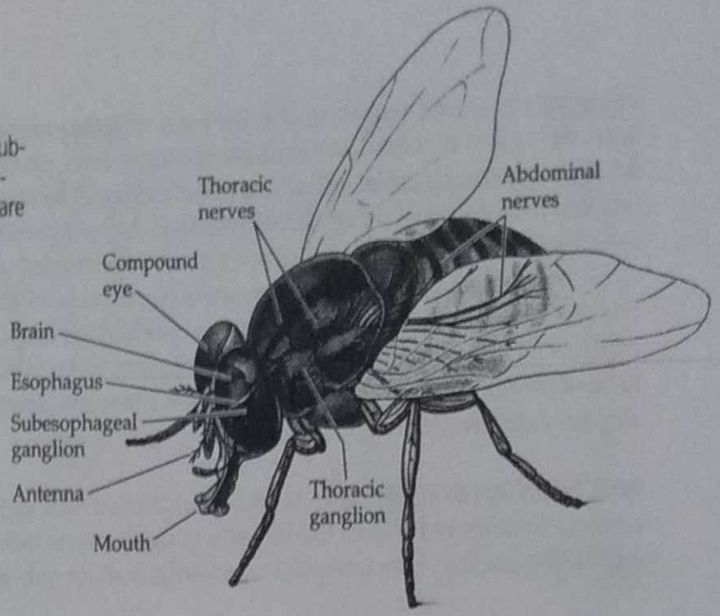
INSECT NERVOUS SYSTEMS Insects are remarkable for their variety of color, form, and presence in different habitats. The life cycle of many insects includes striking morphological changes (e.g., from caterpillar to butterfly) that not only affect the external form

BOX 6.2 Why Should We Study Particular Species?

With all the species that are available, why should we choose certain ones for study? Investigators usually follow several criteria in selecting species for their research. Here are some examples:

1. *Outstanding features.* Some species are champions at various behaviors and abilities, such as sensory discrimination (e.g., the acute auditory localization of the owl, or the extremely fine visual acuity of the eagle) or control of movement (e.g., the flight behavior of the housefly). These abilities are often linked to highly specialized neuronal structures that incorporate and optimize particular designs that may be less conspicuous in other organisms (Bullock, 1984, 1986). Study of such species may yield general principles that apply to other species. The female spotted hyena appears to have a penis and is dominant over the smaller male; this sex "reversal" is caused by unusual hormonal adaptations that help illuminate sexual development (see Box 12.1).
2. *Convenience.* Some species, such as the laboratory rat, are particularly convenient for study because they breed well in the laboratory, are relatively inexpensive to maintain, are not rare or endangered, have relatively short life spans, and have been studied extensively already, so there is a good base of knowledge about them at the outset. In addition, they may serve as good models because their morphology and behavior show clear relationships to other species. Other species are convenient because they offer advantages for certain methods of study. For example, some mollusks have relatively simple nervous systems that aid in tracing neural circuits. The fruit fly *Drosophila* is excellent for genetic studies because it has a relatively simple genome and a short time period between generations; furthermore, investigators have been increasingly impressed by the large number of DNA sequences that *Drosophila* shares with mammals, including humans (R. Lewis, 1998).
3. *Comparison.* Close relationships between species that behave very differently enable the testing of hypotheses. For example, whereas in some closely related species of rodents the home ranges of males and females differ in size, in others they do not. Comparison of these species tests whether differences in maze-solving ability are associated with the size of the home range and with the size of the hippocampus (see Chapter 17).
4. *Preservation.* Studies of rare and/or endangered species can help set priorities and assess options for the conservation of biodiversity (Mace et al., 2003). Endangered species are seldom studied in the laboratory, but they may be investigated in field studies or in zoos.
5. *Economic importance.* Species that are economically important include agricultural animals (e.g., sheep and cows), animals that furnish valuable products (e.g., fishes), predators on agricultural animals (e.g., wolves), or destroyers of crops (e.g., elephants). Studying these animals can provide information that helps increase production and/or decrease losses.
6. *Treatment of disease.* Some species are subject to the same diseases as other species and therefore are valuable models for investigation, For diseases of the nervous system, examples include certain kinds of mice that provide a model for the behavior and anatomy of Down syndrome (see Chapter 7); baboons and certain breeds of dogs that are prone to seizures (see Chapter 3); several breeds of dogs that are afflicted by narcolepsy (see Chapter 14); some strains of rodents that provide models for depression (see Chapter 16); and *Drosophila* and mice, which now provide models for investigations of Parkinson's disease (see Chapter 11).

6.9 The Nervous System of a Typical Insect, *Drosophila melanogaster* In insects, such as this fruit fly, the brain with its subdivisions is linked via bundles of axons (connectives) to groups of ganglia in the thorax and abdomen. The brain, connectives, and ganglia are shown here in blue.



of the animal but also involve a resculpturing of the nervous system. The sensory organs of insects also display great variety and sensitivity.

In spite of the diversity of insect body form (there are over a million living species), the central nervous systems of insects are remarkably similar: They vary "astonishingly little from the most primitive to the most advanced" (Edwards and Palka, 1991, p. 391). The gross outline of the adult insect nervous system consists of a brain in the head end and ganglia in each body segment behind the head (**Figure 6.9**). Bundles of axons connect ganglia to the brain. The number of ganglia varies; in some insects all the ganglia of the chest and abdomen fuse into one major collection of cells. In other insects there are as many as eight ganglia in a chain. The brain itself contains three major compartments: two lobes of the protocerebrum and an optic lobe. The protocerebrum is the most complex part of the insect brain, and its right and left lobes are each continuous with the large optic lobe, an extension of the compound eye. Within the optic lobe are distinct masses of cells that receive input from the eye, as well as from the brain. Electrical stimulation of sites within the protocerebrum elicits complex behaviors.

The relative sizes of different components of the protocerebrum differ among insects, and some of these variations may be particularly relevant to behavioral variations. For example, a portion of the protocerebrum called the *corpus pedunculatum* is especially well developed in social insects, and the behavior of these animals tends to be more elaborate than that displayed by solitary insects.

One prominent feature of the nerve cord of insects is **giant axons**—fibers much bigger in diameter than most. The large diameter of these axons means that they conduct action potentials rapidly (see Chapter 3), making them valuable for sending messages quickly. Some insects have receptive organs (the *cerci*, singular *cercus*) in the tail that detect air movement; these receptors connect to giant interneurons with very large axons that ascend the nerve cord to the head. Along the way, these axons excite some motoneurons. This system originated to allow insects to escape predation by retreating rapidly. In many insects (e.g., cockroaches) this system still functions as an escape system; in other insects the cerci and the connections of the giant interneurons have been modified so that they also play a role in reproductive behavior (in crickets) or help regulate flight maneuvers (in grasshoppers). Whatever its function in a particular species, the basic organization and cellular composition of this system appears to have remained the same for a very long time, perhaps as long as 400 million years (Edwards and Palka, 1991).

Vertebrate and invertebrate nervous systems differ

Let's compare some of the features of vertebrate and invertebrate nervous systems:

- *Basic plan.* All vertebrates and most invertebrates share a basic plan that consists of a central nervous system and a peripheral nervous system.

giant axon A large-diameter axon; found in some invertebrates.

- *Brain.* All vertebrates and many invertebrates, including mollusks and insects, have brains. The general evolutionary trend in both vertebrates and invertebrates is toward increasing brain control over ganglia at lower levels of the body.
- *Number of neurons.* Whereas vertebrate brains usually have many neurons devoted to information processing, invertebrate brains usually have fewer but larger and more-complicated neurons to integrate information.
- *Ganglion structure.* Vertebrate ganglia have the cell bodies on the inside and the dendrites and axons on the outside. Ganglia in invertebrate nervous systems have a different structure: an outer rind of cell bodies and an inner core that consists of the extensions of the cell bodies forming a dense **neuropil** (a network of axons and dendrites).
- *Axons and neural conduction.* Many axons of mammalian neurons are surrounded by myelin, which helps them conduct impulses faster than unmyelinated axons can (see Chapter 3). Invertebrates have no myelin to speed nerve conduction, but as we mentioned in the previous section, many have a few giant axons to convey messages rapidly.
- *Structural changes.* The structure of the nervous system undergoes large-scale changes in some invertebrates during metamorphosis. Vertebrates show important changes in neural structure during development, but these changes are not as dramatic as the changes during invertebrate metamorphoses.
- *Location in the body.* In vertebrates the central nervous system is encased in the bony skull and spinal column. In many invertebrates the nervous system is built around the digestive tract.

The Evolution of Vertebrate Brains Can Be Related to Changes in Behavior

During the course of evolution the characteristics of the nervous system have changed progressively. One especially prominent change in the last 100 million years has been a general tendency for the brain size of vertebrates to increase, and the brains of our human ancestors have shown a particularly striking increase in size over the last 2 million years. How, then, has the evolution of the brain been related to changes in behavioral capacity?

Present-day animals and fossils reveal evolution of the brain

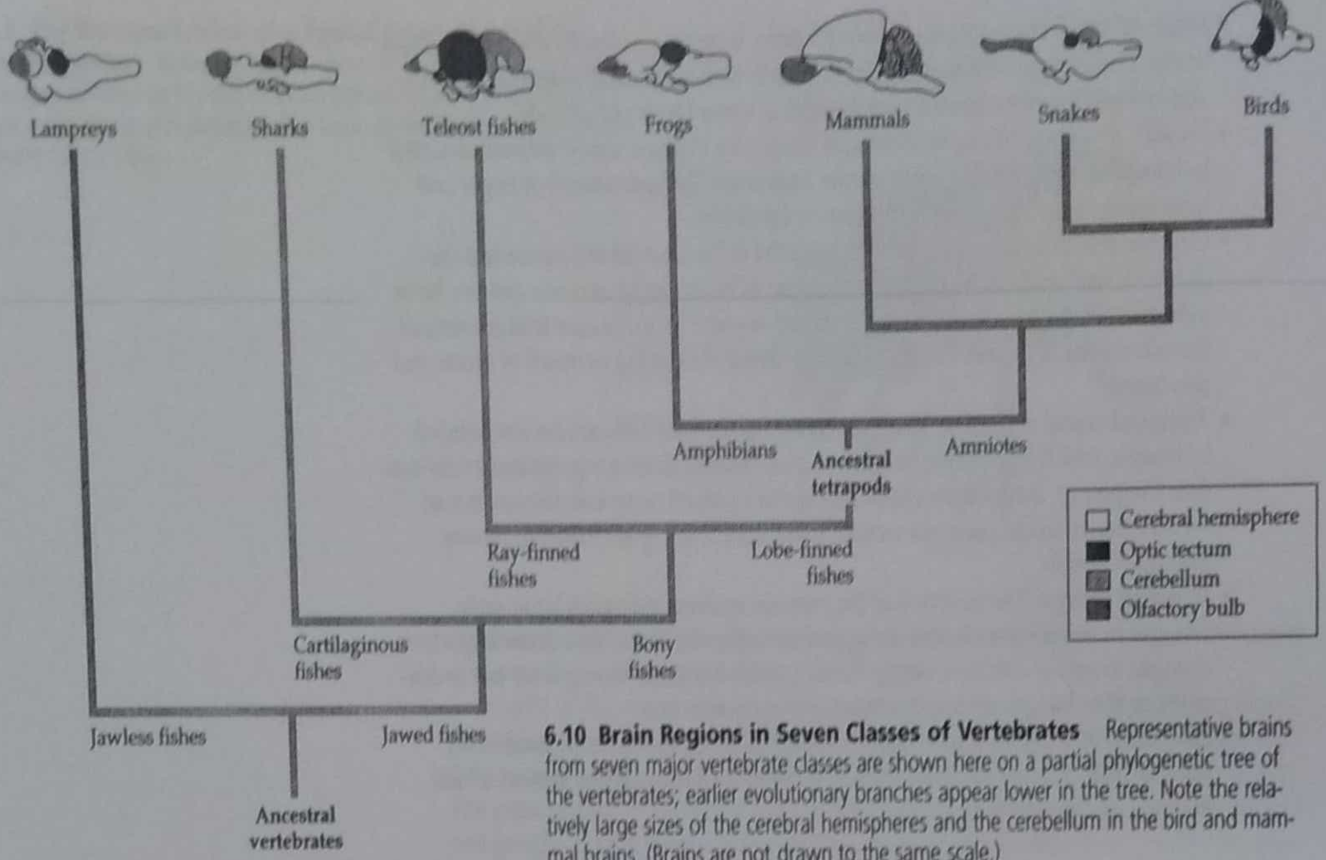
Theoretically we could learn more about the evolution of the brain by studying the brains of fossil animals, but brains themselves do not fossilize—at least, not literally. Two methods of analysis have proved to be helpful. One is to use the cranial cavity of a fossil skull to make a cast of the brain that once occupied that space. These casts (called **endocasts**; the Greek *endon* means "within") give a reasonable indication of the size and shape of the brain, but no fine detail.

The other method is to study present-day animals, choosing species that show various degrees of similarity to (or difference from) ancestral forms. Although no modern animal is an ancestor of any other living form, some present-day species resemble ancestral forms more closely than others do. For example, present-day salamanders are much more similar to vertebrates of 300 million years ago than are any mammals. Among mammals, some species, such as the opossum, resemble fossil mammals of 50 million years ago more than do other species, such as the dog. Thus a species such as the opossum is said to retain primitive or ancestral states of particular anatomical features. Anatomists who study the brains of living species can obtain far more detailed information from such species than from endocasts because they can investigate the internal structure of the brain: its nuclei, fiber tracts, and the circuitry formed by connections of its neurons.

We must be careful not to interpret brain size as if it were a linear evolutionary sequence. The main classes of vertebrates in **Figure 6.10**, for example, represent different

neuropil The conglomeration of dendrites and the synapses upon them.

endocast A cast of the cranial cavity of a skull, especially useful for studying fossils of extinct species.


Lampreys
Sharks
Teleost fishes
Frogs
Mammals
Snakes
Birds
Amphibians
Ancestral tetrapods
Amniotes
Ray-finned fishes
Lobe-finned fishes
Cartilaginous fishes
Bony fishes
Jawless fishes
Jawed fishes
Ancestral vertebrates
☐ Cerebral hemisphere
■ Optic tectum
▨ Cerebellum
■ Olfactory bulb

6.10 Brain Regions in Seven Classes of Vertebrates Representative brains from seven major vertebrate classes are shown here on a partial phylogenetic tree of the vertebrates; earlier evolutionary branches appear lower in the tree. Note the relatively large sizes of the cerebral hemispheres and the cerebellum in the bird and mammal brains. (Brains are not drawn to the same scale.)

lines or radiations of evolution that have been proceeding separately and simultaneously for at least 200 million years. For example, today's sharks have much larger brains than primitive sharks had, but the evolution of large-brained sharks had nothing to do with the development of large brains in mammals. The line of descent that eventually led to mammals had separated from that of the sharks before the large-brained sharks evolved.

Through evolution, vertebrate brains have changed in both size and organization

Let's consider some examples of changes in the size and organization of vertebrate brains. Even the living vertebrate that has the most-primitive features—the lamprey (a jawless fish)—has a more complex brain than it used to be given credit for. The lamprey has not only the basic neural chassis of spinal cord, hindbrain, and midbrain, but also a diencephalon and a telencephalon. Its telencephalon has cerebral hemispheres and other subdivisions that are also found in the mammalian brain. So all vertebrate brains appear to have these regions.

One difference in basic brain structure between the lamprey and other vertebrates is that the cerebellum in the lamprey is very small. The evolution of large cerebellar hemispheres in birds and mammals appears to be a case of independent evolution from the small cerebellum in their common reptilian ancestor; the increased size of the cerebellum may be related to increased complexity of sensory processing and increased motor agility.

The differences among the brains of vertebrate species, then, lie not in the existence of basic subdivisions, but in their relative size and elaboration. At what stages of vertebrate evolution do various brain regions first become important? Large, paired optic lobes in its midbrain probably represent the lamprey's highest level of visual integration. In bony fishes, amphibians, and reptiles, the relatively large optic tectum in the midbrain (see Figure 6.10) is the main brain center for vision. In birds and mammals, however, complex visual perception requires an enlarged telencephalon.

All mammals have a six-layered **isocortex** (from the Greek *iso*, "same," and the Latin *cortex*, "bark of a tree"). The isocortex was formerly called the *neocortex*, but that term is considered outmoded by some. In more-recent mammals the isocortex accounts for more than half the volume of the brain. In mammals the cortex is the structure mainly responsible for many complex functions, such as the perception of objects. Regions of the brain that were responsible for perceptual functions in less-encephalized animals—such as the midbrain optic lobes (in the lamprey) or the midbrain optic center (in the frog)—have in present-day mammals become visual reflex centers. (We will refer to the isocortex or, more simply, the cortex, in almost every chapter in connection with perception and other complex cognitive functions.)

Reptiles were the first vertebrates to exhibit relatively large cerebral hemispheres. Reptiles were also the first vertebrates to have a cerebral cortex, but their cortex has only three layers, unlike the six cortical layers of mammals. Part of the cortex in reptiles may be homologous to the three-layered hippocampus in mammals.

Brain size evolved independently in multiple lineages

The brain is sometimes said to have increased in size with the appearance of each succeeding vertebrate class shown in Figure 6.10, but that statement is wrong in several respects. For one thing, there are exceptions among the present-day representatives of the various classes; for example, birds appeared later than mammals but do not have larger brains than mammals. For another, the generalization arose from the old way of viewing vertebrate evolution: as one linear series of increasing complexity rather than as a series of successive radiations.

If we compare animals of similar body size, we see considerable variation in brain size within each line of evolution. For example, within the ancient class of jawless fishes, the hagfishes, which are more-recent members of that class, have forebrains that are four times as large as those of lampreys of comparable body size. The increase of brain size in relation to behavioral capacity has been studied most thoroughly in the mammals.

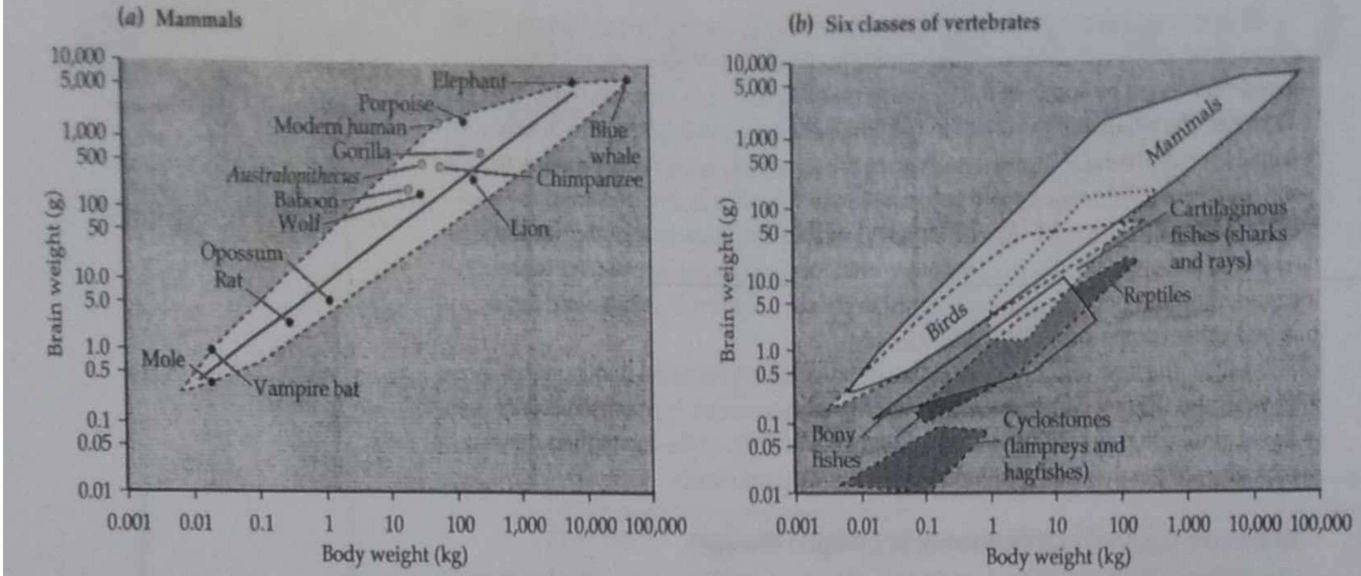
THE ENCEPHALIZATION FACTOR The study of brain size is complicated by the wide range of body sizes, which raises the question, How are body size and brain size related? A general relationship was found first for present-day species and then applied successfully to fossil species. This function turns out to be useful in finding relationships between brain and behavior.

We humans long believed our own brains to be the largest, but this belief was upset in the seventeenth century when the elephant brain was found to weigh three times as much as our own. Later, whale brains were found to be even larger. These findings puzzled scholars, who took it for granted that human beings are the most intelligent of animals and therefore must have the largest brains. To address this apparent discrepancy, they proposed that brain weight should be considered as a fraction of body weight. On this basis humans outrank elephants, whales, and all other animals of large or moderate body size. But a mouse has about the same ratio of brain weight to body weight as a human, and the tiny shrew outranks a human on this measure. Without trying to prove that one species or another is "brainiest," we would like to know how much brain is needed to control and serve a body of a given size. From a comparative point of view, what is the general relation between brain size and body size?

When we plot brain weights and body weights for a large sample of mammals, we see some generalities (**Figure 6.11*a***). All the plot points fall within a narrow polygon. Since both scales are logarithmic, the graph in Figure 6.11*a* encompasses a great variety of animal sizes, and departures from the general rule tend to be minimized. The line drawn through the center of the polygon has a slope of about 0.69 (Harvey and Krebs, 1990).

Let's test the generality of this rule by examining the relation between brain weight and body weight for six vertebrate classes (**Figure 6.11*b***). In each class the data yield a diagonal area with a slope that's about the same, so the relationship between brain weight and body weight is similar for all classes of vertebrates. But notice that the diag-

isocortex Cerebral cortex that is made up of six distinct layers. Formerly referred to as *neocortex*.



(a) Mammals

(b) Six classes of vertebrates

6.11 The Relation between Brain Weight and Body Weight (a) Brain weight is related here to body weight in several mammalian species. Note that both axes are logarithmic, so the graph includes a wide range of brain weights and body weights. A polygon has been drawn to connect the extreme cases and include the whole sample. The diagonal line shows the basic relationship, with brain weight related to the 0.69 power of body weight. (b) Brain weight is plotted here against body weight for various species in six classes of vertebrates. Each class is represented by a polygon that includes a large sample of species in that class. The other classes of animals fall below the mammals, reflecting the fact that, relative to body weight, brain weight is smaller in those classes; they are less "brainy" than the mammals. (Part *a* after H. Stephan et al., 1981; *b* after Jerison, 1991.)

onal areas are displaced from each other vertically in Figure 6.11*b*: the mammals are highest, the bony fishes and reptiles clearly lower, and cyclostomes (e.g., the lamprey) the lowest. This configuration reflects the fact that these classes have successively less brain weight for a body of the same size. Thus a mammal or a bird that weighs about 100 g (e.g., a rat or blue jay) has a brain that weighs about 1 g, but a fish or a reptile of the same body weight has a brain that weighs only a little more than 0.1 g; a 100-g lamprey, for example, has a brain that weighs only about 0.03 g.

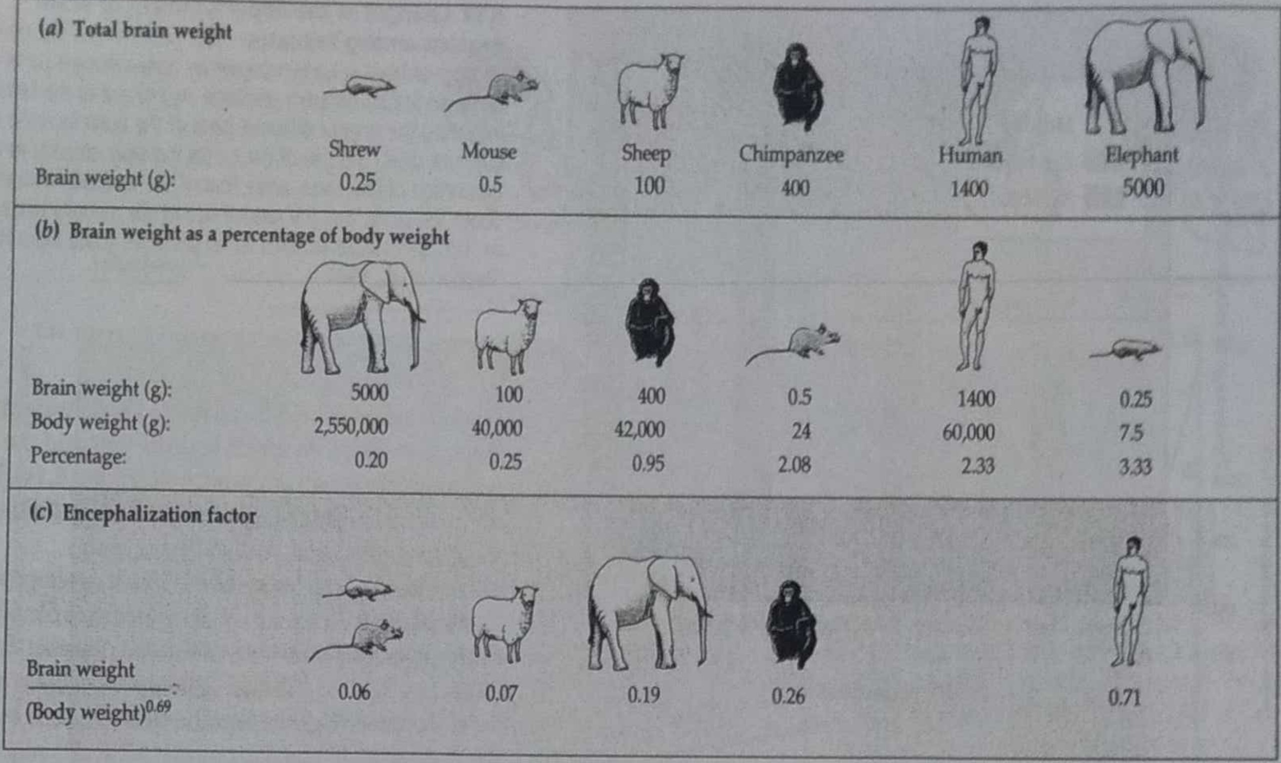
To take into account the variation both between classes and within classes, we need a measure of vertical distance above or below the diagonal line on the graph. This distance is usually called *k* and is different for each class and for each species. Because *k* indicates the relative amount of brain, it is called the **encephalization factor**. The greater the encephalization factor is for a species, the higher its value is above the diagonal line for its class. In Figure 6.11*a* the point for humans is farther from the black diagonal line than is the point for any other species. In terms of the encephalization factor, human beings rate higher than any other species. **Figure 6.12c** gives the values of the encephalization factor for several mammalian species.

Brain size has been studied in many species of vertebrates, both living and fossil. These studies have yielded clues about some selection pressures that have led to larger brains. For example, you may have heard the statement that dinosaurs became extinct because of the inadequacy of their small ("walnut-sized") brains (**Figure 6.13**). Is this hypothesis correct?

Examination of the endocasts of dinosaur brains shows that dinosaur brain weights fit the relationship for reptiles shown in Figure 6.11*b*. For example, the brain of *Tyrannosaurus rex* probably weighed about 700 g—only half the size of the human brain, but much heavier than a walnut and appropriate for a reptile of its size—so it seems unlikely that dinosaurs perished because of a lack of brains (Jerison, 1991). A more likely cause of their demise is climate change, perhaps caused by collision of an asteroid with Earth.

THE EVOLUTION OF BRAIN SIZE As the brain has evolved, it has shown adaptive size changes both in specific regions and overall; this adaptation illustrates both the specificity and the continuity among species that we mentioned in Chapter 1. Certain capabilities, such as foraging for food, have been linked to sizes of particular brain regions, as we saw earlier in this chapter. In contrast, some other capabilities are related to overall cortical volume rather than to the volume of any particular region of cortex; this relationship suggests that some capabilities could improve only as the result of an increase in total cortical volume, although this seems like an inefficient way to add tissue related to a specific function.

encephalization factor A measure of brain size relative to body size.


(a) Total brain weight
Shrew
Mouse
Sheep
Chimpanzee
Human
Elephant
Brain weight (g):
0.25
0.5
100
400
1400
5000
(b) Brain weight as a percentage of body weight
Brain weight (g):
5000
100
400
0.5
1400
0.25
Body weight (g):
2,550,000
40,000
42,000
24
60,000
7.5
Percentage:
0.20
0.25
0.95
2.08
2.33
3.33
(c) Encephalization factor
Brain weight / (Body weight)^0.69:
0.06
0.07
0.19
0.26
0.71

6.12 Who Is the Brainiest? For this sample of small to large mammals, the answer depends on what measure is used: total brain weight (*a*), brain weight as a percentage of body weight (*b*), or the encephalization factor (*c*). For each measure, the animals are ranked here from lowest value to highest.

The conclusion that changes occur in the overall size of the brain rather than in specific brain regions is consistent with the concept that overall developmental factors and programs (which we will consider in Chapter 7) severely constrain the magnitude of local adaptations. Supporting this conclusion is the finding that, if the weight of the brain of any mammalian species is known, the weight of each of its parts can be predicted (Finlay and Darlington, 1995).

To study this relationship, Finlay and Darlington used data published by H. Stephan et al. (1981) on sizes of the main parts of the brain in 131 species of mammals: insectivores, bats, prosimians, and simians (including *Homo sapiens*). Their data set has the advantages, for comparative study, of including a large number of species, a wide range of ecological niches (including terrestrial, arboreal [tree-dwelling], burrowing, amphibious, and flying), and a wide range of body weights (2–105,000 g) and brain sizes (60–1,252,000 mm^3). Another advantage is the fact that the 11 brain divisions measured constitute the entire brain.

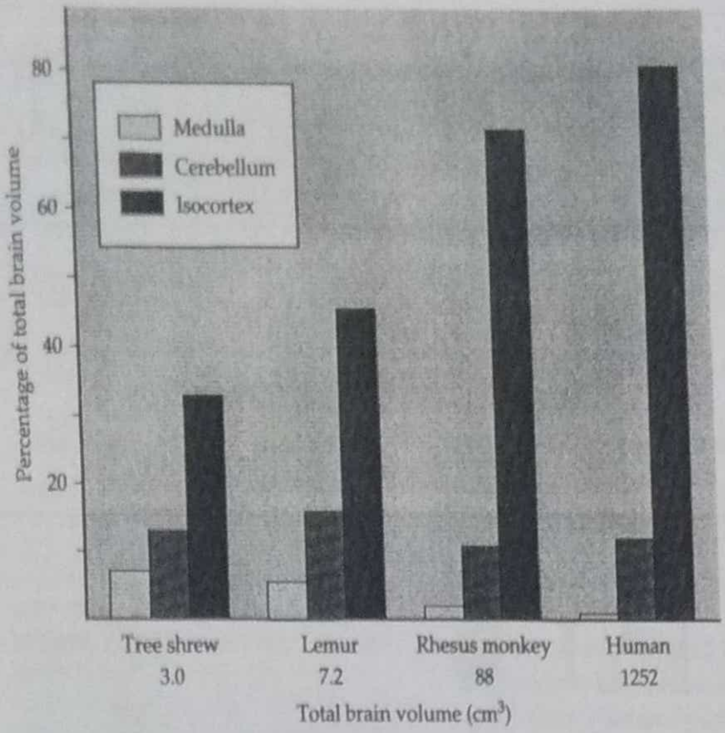
In logarithmic scales, the size of each brain structure showed a highly linear relation to brain weight and correlated 0.96 or higher with total brain size. Thus a simple rule relates the size of the particular structure to total brain size for all parts of the brain. The exception is the olfactory bulb, which has a much larger relative size in some species, presumably because evolution has favored a very sensitive sense of smell in those species.

Although most parts of the brain increase roughly in proportion to total increases in brain size, the rates of increase show subtle differences. In a comparison of primate brains from small to large, the

THE FAR SIDE By GARY LARSON
11-7
Larson
The Far Side, © 1989 FarWorks, Inc. Reprinted with permission. All rights reserved.

"The picture's pretty bleak, gentlemen... The world's climates are changing, the mammals are taking over, and we all have a brain about the size of a walnut."

6.13 Was the Dinosaur Being Too Modest?



6.14 Changes in the Apportionment of Brain Regions among Primates This graph shows the percentage of brain volume occupied by three different parts of the brain in four different primates. As the size of the brain increases, the sizes of different parts of the brain increase at different rates. The size of the cortex increases steadily as a proportion of brain size, while that of the cerebellum stays about the same, and the relative size of the medulla decreases. This generalization holds for all primates. (Data from H. Stephan et al., 1981.)

medulla becomes smaller relative to brain weight, the cerebellum keeps pace with brain weight, and the cortex grows more than any other part (**Figure 6.14**). Thus the proportion of brain devoted to each part differs in important ways from small to large brains.

The fact that the brain shows overall developmental constraints—with the size of most structures correlating highly with total brain size—does not contradict the existence of some specific size adaptations of brain structures. For one thing, the logarithmic scales used by Finlay and Darlington tend to obscure subtle differences, so even a threefold increase or decrease in the size of a region is hardly noticed. For another thing, the brain divisions analyzed by Finlay and Darlington are relatively large, and most of them contain subdivisions that may vary in size. For example, one of the brain divisions in their study is the mesencephalon, which includes both the inferior colliculus and the superior colliculus; as we have mentioned, the inferior colliculus is larger in animals that depend mainly on audition, whereas the superior colliculus is larger in animals that rely on vision. So although general constraints on development are strong, different regions of the brain do exhibit specific adaptations.

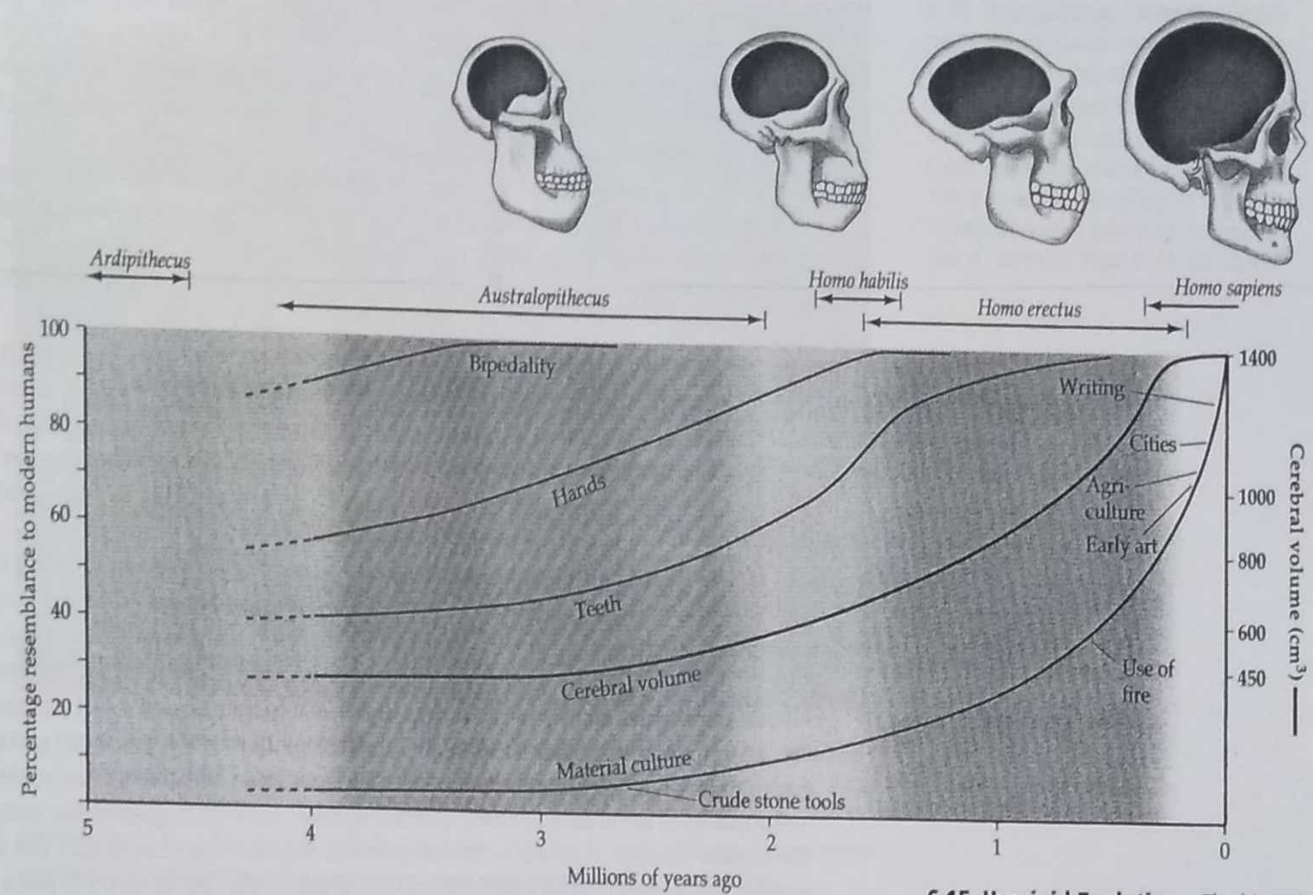
THE RAPID EVOLUTION OF HOMINID BRAINS Valuable information about evolutionary relationships between brain and behavior comes from the study of hominids—primates of the family Hominidae—of which we humans are the only living species. Such studies shed light on our distant ancestors and help us understand how the body adapts to the environment through natural selection.

The structural and behavioral features that we consider characteristic of humans did not develop simultaneously (Falk, 1993). Our large brain is a relatively late development. According to one estimate, the trunk and arms of hominids reached their present form about 10 million years ago. Hominids began walking on two feet more than 4 million years ago, and the oldest manufactured stone tools date back to about 2.6 million years ago. (Note that not all authorities agree on these dates; they should be considered only approximate.)

The early toolmakers and users were bipedal hominids called **australopithecines**. Endocasts of their skulls show a brain volume of about 350 to 400 cm^3 (**Figure 6.15**), about the size of the modern chimpanzee brain. Chimpanzees do not make tools from stone, although some collect stones to use as tools, and one captive chimpanzee has been taught to make stone tools. But the australopithecines made and used crude stone tools in hunting and in breaking animal bones to eat. The ability to use tools reduced the selection pressure to maintain large jaws and teeth, and hominid jaws and teeth thus became steadily smaller than the ape's and more like those of modern human beings. Smaller teeth may also be related to increasing social tolerance, since canine teeth are often used in fighting among primate groups.

Even though their brains did not grow much, never becoming larger than 600 cm^3, our australopithecine ancestors were successful animals, lasting—relatively un-

australopithecine Of or related to *Australopithecus*, a primate genus, known only from the fossil record, thought to be an ancestor to humans.



6.15 Hominid Evolution The bipedal (two-footed) gait was similar to that of modern humans even in *Australopithecus*, but cerebral volume reached its current size only in *Homo sapiens*. High culture (art, agriculture, cities, writing) emerged only relatively recently and was not associated with any further change in brain size. (After Tobias, 1980; updated with the assistance of Tim White.)

changed—some 2 million years. Examination of ancient campsites suggests that these early hominids lived in nomadic groups of 20 to 50 individuals. They hunted and gathered plant foods—a new lifestyle that was continued by later hominids.

About 1.5 to 2 million years ago, when the australopithecines died out, *Homo erectus* appeared (see Figure 6.15). This early representative of the genus *Homo* started with a cranial capacity of about 700 cm^3 and a smaller face than *Australopithecus* had. As *Homo erectus* evolved, the brain became steadily larger, reaching the present-day volume of about 1400 cm^3, and the face continued to become smaller. *Homo erectus* made elaborate stone tools, used fire, and killed large animals. Fossils and tools of *Homo erectus* are found throughout three continents, whereas those of the australopithecines are found only in Africa. *Homo erectus* may have represented a level of capacity and of cultural adaptation that allowed the hominids to expand into new environmental niches and to overcome barriers that kept earlier hominids in a narrower range.

Evolution of the brain and increased behavioral capacity advanced rapidly during the time of *Homo erectus* (see Figure 6.15). By the time *Homo sapiens* appeared, about 150,000 years ago, brain volume had reached the modern level. Thus, after remaining little changed in size during about 2 million years of tool use by the australopithecines, the hominid brain almost tripled in volume during the next 1.5 million years.

The size of the human brain now appears to be at a plateau. The recent changes in human lifestyle shown in Figure 6.15—such as the appearance of language, the introduction of agriculture and animal husbandry (about 10,000 years ago), and urban living (the last few thousand years)—have all been accomplished and assimilated by a brain that does not seem to have altered in size since *Homo sapiens* appeared. The lack of further increase in brain size may be related to the costs of a large brain, a topic we consider next.

THE COSTS OF A LARGE BRAIN Having a large brain entails costs as well as benefits. Growth of a large brain requires a long gestation period, which is a burden on the mother, and childbirth is difficult because of the large size of the baby's head. Much of the growth of the brain continues during the years after birth, which means prolonged dependence of the infant and prolonged parental care. Although the brain makes up only about 2% of our total adult body weight, when we are at rest it consumes a much bigger proportion of our metabolic budget.

Construction of the human brain is so complex that more than half of our genes contribute to the task. The complex genetic messages that are generated are vulnerable to accidents; mutations of any of them are likely to lead to behavioral disorders. The evolution of large brains is especially remarkable when viewed in the context of these costs.

SELECTION PRESSURES FOR INCREASED BRAIN SIZE A change in any organ during evolution suggests that the change confers advantages with respect to survival. A rapid increase, as in the size of the hominid brain, implies strong advantages for survival. However tiny the differences are between the genes of humans and chimpanzees, they have brought a big difference in brain size. What is the adaptive advantage of having such big brains?

One hypothesis is that selection pressure in the social domain may have led to increased brain size. Tool use is not very widespread in primates, but primates are extremely skilled in a variety of social interactions, such as cooperation, deception, and reciprocity. Anthropologist Robin Dunbar (1993) found a positive relationship between (1) group size in primates and (2) the size of cortex relative to the size of the brain. On the basis of this relationship, Dunbar estimated the maximum size of social group for each species of primate. For humans, this value was about 150. Dunbar inspected the anthropological literature and found that this number came up frequently. For example, the average number of people in hunter-gatherer societies was close to 150. The same number holds true for many functional military units. So the ratio of cortex to brain may indicate the maximum number of individuals with whom we can have a meaningful social relationship.

INNOVATION, TOOL USE, SOCIAL LEARNING, AND ENHANCED BRAIN SIZE IN PRIMATES A major study correlated brain size in 116 species of primates with three different factors that have been proposed to account for the enhanced size of primate brains: (1) innovations in behavior, (2) use of tools, and (3) social learning—that is, learning by observing others (Reader and Laland, 2002). Rather than testing animals for these traits or observing them directly, Reader and Laland surveyed about 1000 articles in primate journals and other relevant literature and found 533 instances of innovation, 607 episodes of tool use, and 445 observations of social learning (**Figure 6.16**). The frequencies were corrected for the amount of research effort spent on each species. In addition to using total brain weights, Reader and Laland used the ratio of what has been called the *executive brain* (the sum of cortex and striatum) to the brainstem (the sum of mesencephalon and medulla).

Both brain measures correlated positively with the frequency of each of the behavioral indices, indicating that each of the behavioral factors is related to expansion of the primate brain. Thus the results indicate that multiple sources of selection favored evolution of the large primate brain.

BRAIN SIZE PREDICTS SUCCESS IN ADAPTING TO A NOVEL ENVIRONMENT We have seen that brain size correlates with the ability to find new ways to obtain food and with group size in primates, but can one test the hypothesis that enlarged brains have evolved as an adaptation to cope with novel or altered environmental conditions? One way would be to introduce species with relatively large or small brains into novel environments and see whether they were able to establish themselves and thrive. Experimental introductions of species into novel environments are not considered ethical, because of problems that often occur when nonindigenous species are introduced. An alternative is to study the rich record of past human-mediated introductions. A recent study that used a global database to examine more than 600 examples of introduction involving 195 bird

6.16 Transmitting Culture Culture has been observed in nonhuman primates. For example, a population of Japanese macaques developed a set of behaviors that included washing food, playing in the water, and eating marine food items, and they transmitted this culture of water-related behaviors from generation to generation. (Courtesy of Frans B. M. de Waal.)

species found that the species with larger brains, relative to body size, tend to be more successful in establishing themselves in novel environments (Sol et al., 2005).

Here are four examples, first for two relatively small-brained species and then for two relatively large-brained species: Many attempts have been made to introduce the chukar partridge (*Alectoris chukar*) as a game bird in different parts of the world, but most attempts have failed. Attempts to introduce the nightingale (*Luscinia megarhynchos*) for aesthetic reasons have failed. On the other hand, attempts to introduce the relatively large-brained rose-ringed parakeet (*Psittacula kramen*) for aesthetic reasons have succeeded in many parts of the world. So have attempts to introduce the barn owl (*Tyto alba*) to control rats.

SEXUAL SELECTION AND BRAIN SIZE Using a different approach, we can evaluate the rapid expansion of the human brain over the last 1.5 million years in terms of Darwin's second evolutionary principle: sexual selection. Geoffrey Miller (2000) suggests that natural selection to obtain food and shelter is not likely to account completely for the large brain and complex intelligence of *Homo sapiens*. In fact, he notes, brain size tripled in our ancestors between 2.5 million years ago and 200,000 years ago, yet during this period our ancestors continued to make the same kind of stone ax. Only *after* the human brain stopped expanding did technological progress develop, so brain growth did not correlate well with the supposed survival benefit of enlarged brains.

Rather, Miller proposes an additional factor to account for large human brains: in humans, he postulates, much creativity, along with related brain growth, is due to sexual selection for abilities to attract attention, stimulate, and surprise a potential mate. This hypothesis, Miller claims, has the further value of presenting an evolutionary theory for such characteristic human traits as humor, art, music, language, and creativity (**Box 6.3**).

The hypothesis that sexual selection for artistry and creativity may lead to increased brain size is supported by recent findings from the family of bowerbirds (Ptilonorhynchidae). To attract and impress females, male bowerbirds construct elaborate structures of twigs, decorated with colorful objects such as shiny beetles, shells, and petals (**Figure 6.17**). Zoologist Joah Madden found that bowerbirds have large brains, compared with other birds (Madden, 2001). Even within the bowerbirds, species that build more-elaborate bowers have larger brains.

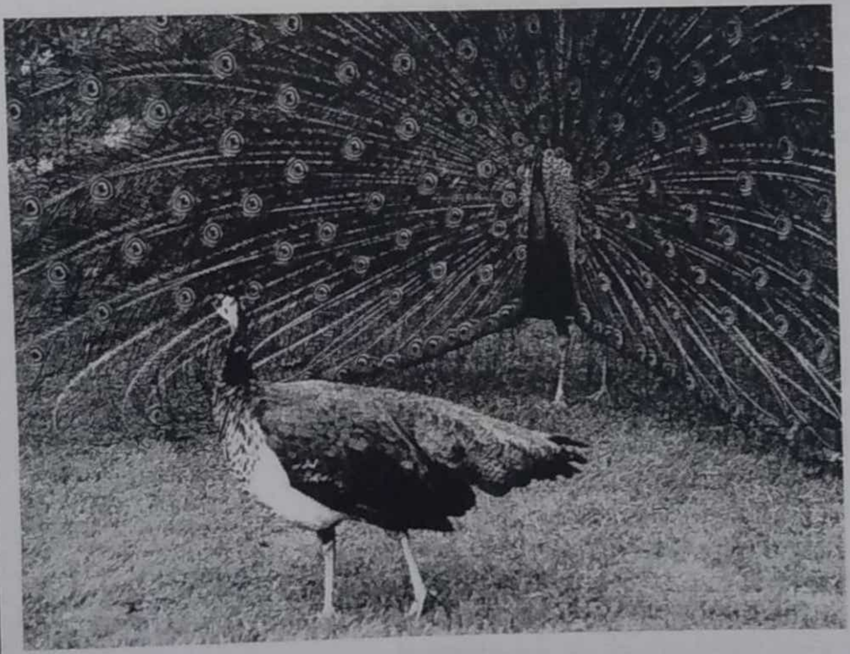
BOX 6.3 Evolutionary Psychology

There's no doubt that humans looking for a mate find some traits more attractive than others, and in other species such sexual selection has been used to explain, for example, why males tend to be larger than females in many species, or why in many bird species the males sing more elaborate songs and are more brightly colored than the females (see the figure). So speculation about selective pressure on reproductive behavior in various animals leads inevitably to questions about the extent to which our own behaviors have been affected by the difference between male and female reproductive strategies:

- *Are women inherently more selective than men about choosing mating partners?* Such a difference could be a result of the tremendous investment of time, energy, and resources that a female mammal must make in each offspring.
- *Are men more promiscuous than women?* It's easy to imagine that the low cost of producing sperm (and the potential for a man to expend no energy on child rearing) might favor such behavior.
- *Do romantic relationships tend to sour after about 7 years?* If so, the reason for this tendency may be that, in the ancestral environment in which hominids evolved, periodically selecting a new mate provided insurance that genetic defects from any one mate would not affect all of the offspring. Was 7 years how long it took for a couple to raise a child to self-sufficiency?
- *Is there an "ideal" waist-to-hip ratio that indicates maximal fertility in women?* Correlational studies suggest that a particular ratio is especially attractive to men, across different cultures and historical eras (Singh, 2002).
- *Are women attracted to power, and men to youth, because natural selection favored these preferences?*

Such speculations have given rise to a lively and controversial field called *evolutionary psychology* (Barkow et al., 1992; Buss, 2000). It's easy to spin plausible tales about how evolution might have shaped our behavior, but the challenge for theorists is to come up with ways to test and potentially disprove these hypotheses. Such an enterprise is especially daunting when ethical considerations mean that the investigator can never manipulate the variables ("Let's see. I'd like you to marry that person over there, and then I'll ask you some questions 7 years from now."), but must rely on correlations and surveys.

Geoffrey Miller (2000) proposes that sexual selection was crucial for evolution of the human brain. If, among early hominids, people came to favor mates who sang, made jokes, or produced artistic works, then such high-order functioning would rapidly evolve in an arms race, as the ever more discriminating brains of one sex demanded ever more impressive performances from the brains of the other sex. Did humor, song, and art originate from the drive to be sexually attractive? And does sexual selection account for the large size of the human brain?



This brightly colored peacock must impress the plain-colored peahen before she will accept his sperm.

PRIMATE SPECIES DIFFER IN GENE EXPRESSION At the start of this chapter we asked why humans and chimpanzees, which are identical in 99% of their genomic DNA sequences, differ in many morphological, behavioral, and cognitive aspects. One answer is that some genes affect brain development more than others. For example, the gene *ASPM* influences the size of the cerebral cortex, and the fact that the protein encoded by the

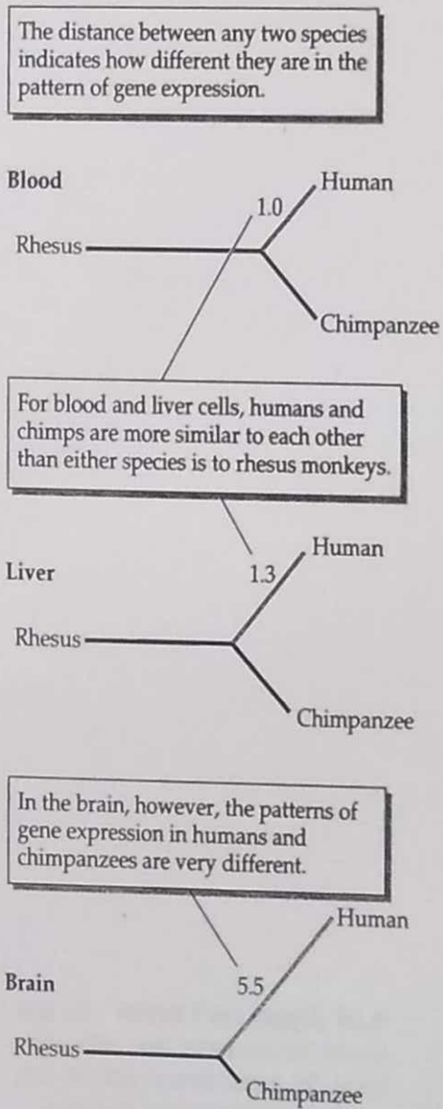
6.17 Bowerbird Nests To attract mates, male bowerbirds build elaborate bowers of twigs, such as this structure, and decorate them with colorful objects. The architectural complexity and ornate decoration of the bowers may be the reason for the relatively large brains of bowerbirds.

gene differs considerably between humans and chimps suggests that *ASPM* evolved rapidly in the line leading to humans (P. D. Evans et al., 2004). So even moderate changes in just a few crucial genes may make a big difference.

Another means by which similar genomes can produce different brains is in the way the genes are *expressed*. Even small changes in DNA can result in big differences in when and where the gene is transcribed to produce its encoded protein. Researchers report that humans differ considerably from other primates in gene expression in the brain (Enard, Khaitovich et al., 2002). To study this question, the investigators measured mRNA and protein expression patterns in brain, liver, and blood cells in humans and other primates. They could then quantify how similar or different two species are in the pattern of genes expressed in particular tissues.

As **Figure 6.18** shows, for blood cells and liver cells, humans and chimpanzees are more similar to each other than either species is to rhesus monkeys. These relationships probably reflect the well-documented evolutionary relationships among the three species. A comparison of the pattern of gene expression in the *brain*, however, shows that we are more different from chimpanzees than they are from monkeys. These observations suggest that the pattern of gene expression in the brain has changed considerably, presumably under selective pressure, since we shared a common ancestor with chimpanzees. Thus the rate of evolutionary change in gene expression in the brain is accelerated in the human lineage relative to the chimpanzee and to other primates, whereas no such acceleration is evident in the liver or blood. The differences between humans and their closest relatives probably reflect not only differences in their DNA *sequences* but also in how those genes are *expressed* to construct a complex brain.

Even a small change in gene expression can cause a dramatic difference in brain development (Chenn and Walsh, 2002). For example, overexpression of just one gene in mice caused so much growth in the cortex that the normally smooth surface developed gyri and sulci (**Figure 6.19**). To answer the question we raised at the start of this chapter, the pattern of gene expression has a tremendous effect on the developing brain and may be what makes humans unique.



The distance between any two species indicates how different they are in the pattern of gene expression.

For blood and liver cells, humans and chimps are more similar to each other than either species is to rhesus monkeys.

In the brain, however, the patterns of gene expression in humans and chimpanzees are very different.

6.18 Differences in Gene Expression in Various Tissues (Enard, Khaitovich et al., 2002.)

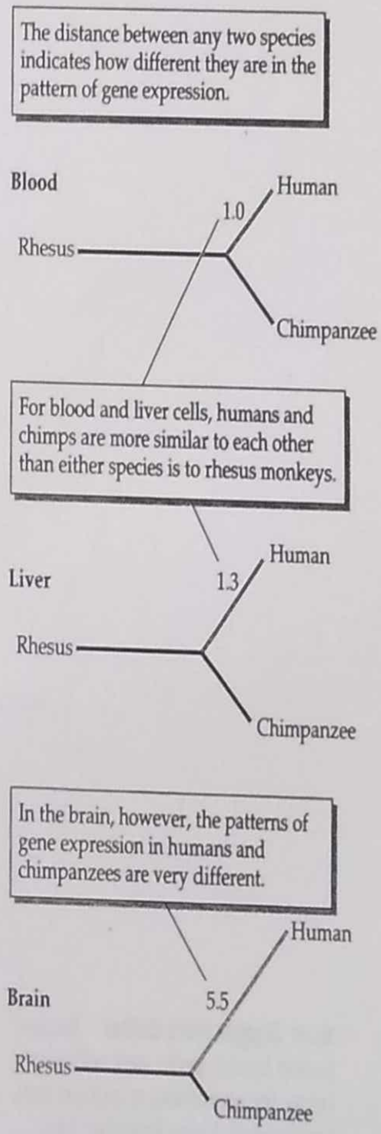
6.17 Bowerbird Nests To attract mates, male bowerbirds build elaborate bowers of twigs, such as this structure, and decorate them with colorful objects. The architectural complexity and ornate decoration of the bowers may be the reason for the relatively large brains of bowerbirds.

gene differs considerably between humans and chimps suggests that *ASPM* evolved rapidly in the line leading to humans (P. D. Evans et al., 2004). So even moderate changes in just a few crucial genes may make a big difference.

Another means by which similar genomes can produce different brains is in the way the genes are *expressed*. Even small changes in DNA can result in big differences in when and where the gene is transcribed to produce its encoded protein. Researchers report that humans differ considerably from other primates in gene expression in the brain (Enard, Khaitovich et al., 2002). To study this question, the investigators measured mRNA and protein expression patterns in brain, liver, and blood cells in humans and other primates. They could then quantify how similar or different two species are in the pattern of genes expressed in particular tissues.

As **Figure 6.18** shows, for blood cells and liver cells, humans and chimpanzees are more similar to each other than either species is to rhesus monkeys. These relationships probably reflect the well-documented evolutionary relationships among the three species. A comparison of the pattern of gene expression in the *brain*, however, shows that we are more different from chimpanzees than they are from monkeys. These observations suggest that the pattern of gene expression in the brain has changed considerably, presumably under selective pressure, since we shared a common ancestor with chimpanzees. Thus the rate of evolutionary change in gene expression in the brain is accelerated in the human lineage relative to the chimpanzee and to other primates, whereas no such acceleration is evident in the liver or blood. The differences between humans and their closest relatives probably reflect not only differences in their DNA *sequences* but also in how those genes are *expressed* to construct a complex brain.

Even a small change in gene expression can cause a dramatic difference in brain development (Chenn and Walsh, 2002). For example, overexpression of just one gene in mice caused so much more growth in the cortex that the normally smooth surface developed gyri and sulci (**Figure 6.19**). To answer the question we raised at the start of this chapter, the pattern of gene expression has a tremendous effect on the developing brain and may be what makes humans unique.

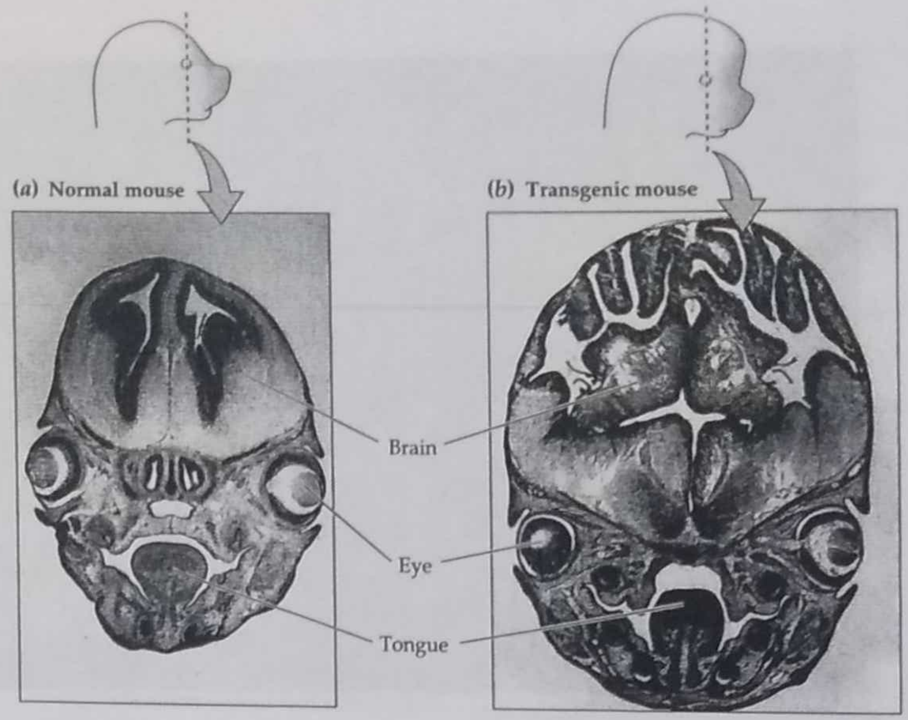


The distance between any two species indicates how different they are in the pattern of gene expression.

For blood and liver cells, humans and chimps are more similar to each other than either species is to rhesus monkeys.

In the brain, however, the patterns of gene expression in humans and chimpanzees are very different.

6.18 Differences in Gene Expression in Various Tissues (Enard, Khaitovich et al., 2002.)

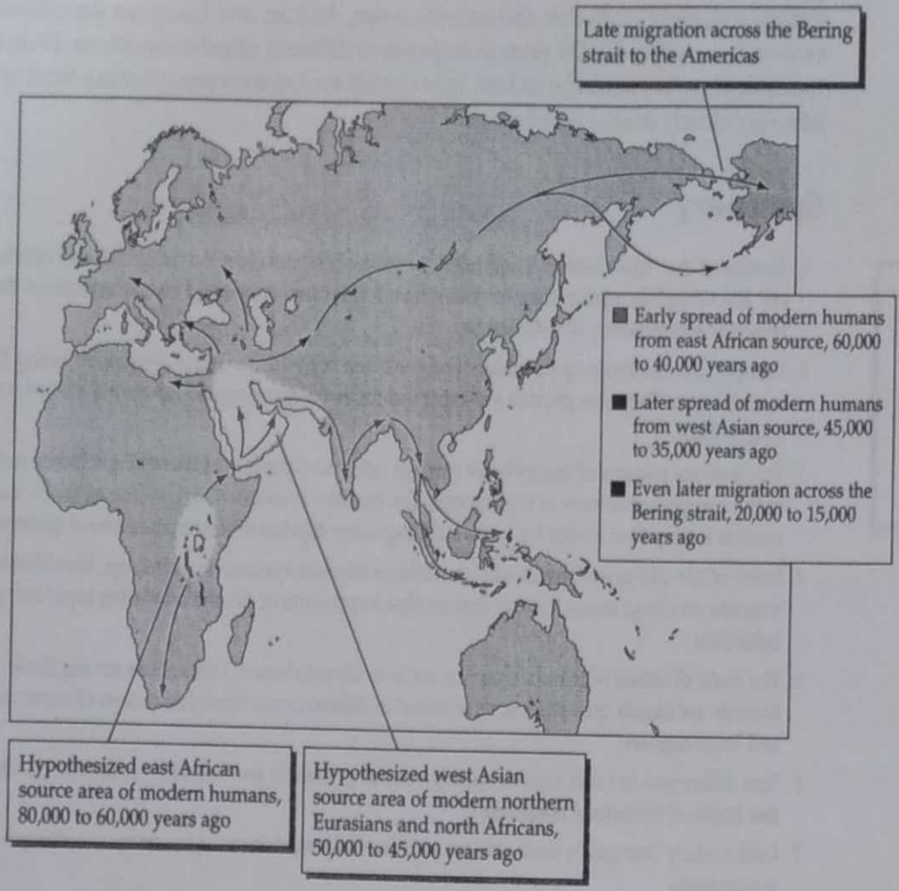


6.19 Over Your Head Normally, mice at birth have a fairly simple cortex with no sulci or gyri (*a*), but increasing the expression of just one gene (that for β-catenin) in transgenic mice results in a monstrously complex, highly folded cortex (*b*). (From Chenn and Walsh 2002; photographs courtesy of Anjen Chenn.)

Evolution Continues Today

Although some examples of evolution have occurred slowly—over millions of years, as shown by the aspects of hominid evolution illustrated in Figure 6.15—other examples occur in a matter of years or decades. These rapid instances of evolution would have surprised Darwin, who thought that natural selection required vast periods of time to be effective. In some cases, selection is driven by natural causes. Other cases of rapid evolution are driven by human behavior, as reviewed by Holmes (2005). For example, use of antibiotic medicines eliminates all but a very few resistant bacteria, but overuse of antibiotics speeds the evolution of resistant bacteria.

6.20 Bigger Isn't Better Because human hunters perfer rams with large horns, the populations of bighorn rams has changed. Males these days have smaller horns than males a few decades ago. This is a disturbing example of evolution in action.


Late migration across the Bering strait to the Americas
▨ Early spread of modern humans from east African source, 60,000 to 40,000 years ago
■ Later spread of modern humans from west Asian source, 45,000 to 35,000 years ago
■ Even later migration across the Bering strait, 20,000 to 15,000 years ago
Hypothesized east African source area of modern humans, 80,000 to 60,000 years ago
Hypothesized west Asian source area of modern northern Eurasians and north Africans, 50,000 to 45,000 years ago

6.21 The Colonization of Europe and Asia by *Homo sapiens* Ages of *Homo sapiens* fossils, in thousands of years. (After Goebel 2007.)

A striking example of evolution in action is the case of bighorn rams in the Rocky Mountains of Alberta, Canada (**Figure 6.20**). The massive curling horns of these rams make them a prized hunting trophy. The rams become legal targets only after their horns reach an almost 360° curl. In some areas of Alberta, most rams are shot within a year or two after reaching this status. As a result, selection has worked in favor of rams whose horns never reach trophy status. In fact, the average horn size has dropped by about 25% over the past 30 years (Coltman et al., 2003).

Darwin's finches are continuing to evolve in the Galápagos Islands. Since 1973, ecologists Peter and Rosemary Grant have spent part of each year studying and measuring all the finches on a small Galápagos island (P. R. Grant and Grant, 2006). For decades the medium ground finch (*Geospiza fortis*) predominated on this island, eating both large and small seeds. Then, in 1982, a breeding population of the large ground finch (*G. magnirostris*) became established on the island. These larger birds eat large seeds more easily than the medium finches can, even those with relatively large beaks. For two decades there were not enough of the larger species to make much difference. But then in 2004, a drought sharply reduced the food supply. Competition for larger seeds became severe, and many of the medium finches with larger beaks died off. The smaller-beaked medium finches, however, survived and passed along the small-beaked trait to their offspring.

An economically important case of recent evolution concerns commercial fishing. In many regions, fishermen are allowed to keep only fish that are larger than a particular size. Atlantic cod off the coast of Newfoundland have been maturing at smaller sizes over several decades, probably because the largest fish are the ones being captured (E. M. Olsen et al., 2004). The remaining small fish produce fewer eggs than large fish, and this reduced egg production could help explain the collapse in the cod population.

New developments in radiocarbon dating have shown that the colonization of Europe and Asia by *Homo sapiens* was more rapid than previously believed (Mellars, 2006), occurring less than 50,000 years ago (**Figure 6.21**). Thus the differences in skin color, stature, and facial traits that characterize Asian, African, and European populations evolved in less than 50,000 years in response to different climatic conditions. Human variation, then, is a reminder of both how quickly evolutionary processes can work and how very closely related we all are.

Summary

1. Studies of the classification of animals help determine how closely related different species are. Knowing this relationship, in turn, helps us interpret similarities and differences in the behavior and structure of different species.
2. Comparative studies help us understand the evolution of the nervous system, including the human brain. They also provide a perspective for understanding species-typical behavioral adaptations.
3. The nervous systems of invertebrate animals range in complexity from a simple nerve net to the complex structures of the octopus. The nervous systems of certain invertebrates may provide a simplified model for understanding some aspects of vertebrate nervous systems.
4. Some of the distinctive features of invertebrate nervous systems include large, identifiable neurons and large axons that are frequently components of circuits mediating rapid escape behaviors.
5. The main divisions of the brain are the same in all vertebrates. Differences among these animals are largely quantitative, as reflected in differences in the relative sizes of nerve cells and brain regions.
6. Size differences in brain regions among various mammals are frequently related to distinctive forms of behavioral adaptation.
7. Evolutionary changes in brain size are apparent in comparisons of fossils and contemporary animals.
8. The brain size of a species must be interpreted in terms of body size. The overall rule for vertebrates is that brain weight is proportional to the 0.69 power of body weight.
9. Some animals have larger brains and some have smaller brains than the general relation between brain and body weights predicts; that is, they differ in encephalization factor. Humans, in particular, have larger brains than their body size would predict.
10. Within each of the lines of vertebrate evolution, relative brain size varies, and the more recently evolved species usually have the larger encephalization factors.
11. Not only natural selection, but also sexual selection, has been proposed to account for the large size of the human brain.
12. Differences between humans and their nearest evolutionary relatives, the chimpanzees, reflect not only the small differences in their genomic DNA sequences but also differences in gene expression patterns. Humans differ from other primates especially in the large number of genes expressed in the brain.
13. Evolution continues today in both human beings and nonhuman species.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

Recommended Reading

Alcock, J. A. (2005). *Animal behavior: An evolutionary approach* (8th ed.). Sunderland, MA: Sinauer.

De Waal, F. (2001). *The ape and the sushi master.* New York: Basic Books.

Graur, D., and Li, W. (1999). *Fundamentals of molecular evolution* (2nd ed.). Sunderland, MA: Sinauer.

Miller, G. F. (2000). *The mating mind: How sexual choice shaped the evolution of human nature.* New York: Doubleday.

Streidter, G. P. (2004). *Principles of brain evolution.* Sunderland, MA: Sinauer.

Understanding evolution, http://evolution.berkeley.edu.

CHAPTER 7

CONTENTS

Growth and Development of the Brain Are Orderly Processes 181

Development of the Nervous System Can Be Divided into Six Distinct Stages 182

Glial Cells Provide Myelin, Which Is Vital for Brain Function 197

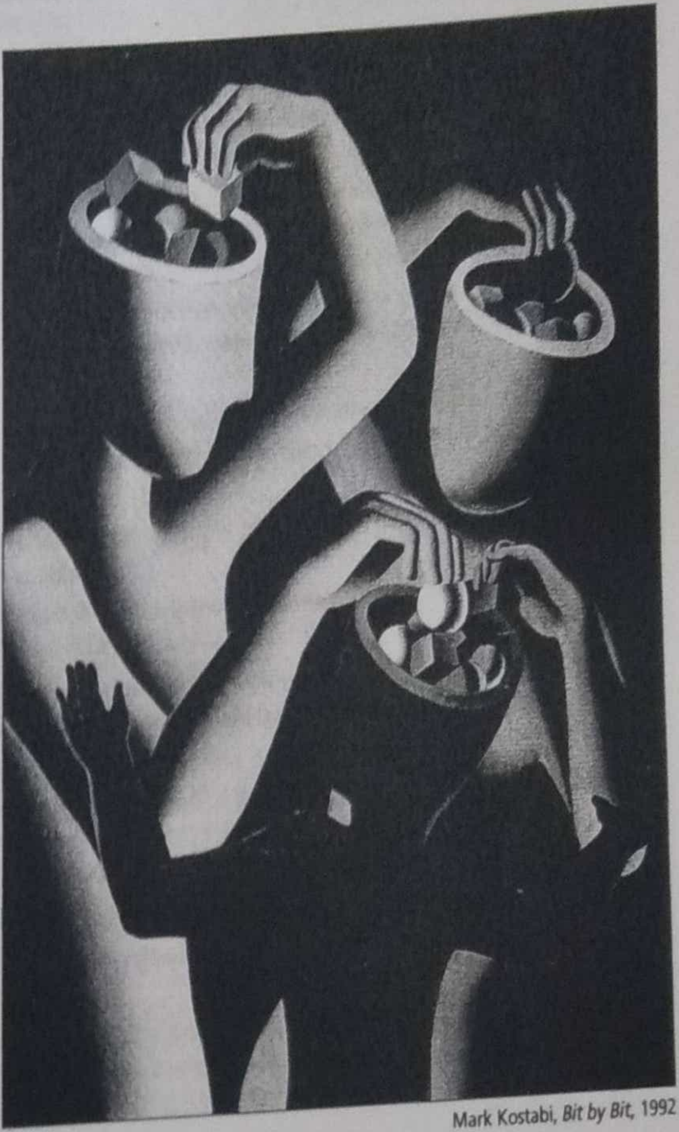
Genes Interact with Experience to Guide Brain Development 198

Experience Is an Important Influence on Brain Development 202

Developmental Disorders of the Brain Impair Behavior 206

The Brain Continues to Change As We Grow Older 210

Two Timescales Are Needed to Describe Brain Development 213



Mark Kostabi, *Bit by Bit*, 1992

Life-Span Development of the Brain and Behavior

Overcoming Blindness

As a 3-year-old, Michael May was injured by a chemical explosion that destroyed his left eye and damaged the surface of his right eye so badly that he was blind. He could tell whether it was day or night, but otherwise he couldn't see anything. An early attempt to restore his sight with corneal transplants failed, but Michael seemed undaunted. He learned to play Ping-Pong using his hearing alone (but only using the table at his parent's house, where he learned to interpret the sound cues). Michael also enjoyed riding a bicycle, until his parents made him stop after he crashed his brother's and his sister's bikes.

As an adult, Michael became a champion skier, marrying his instructor and raising two sons. He also started his own company, making equipment to help blind people navigate on their own.

Then, when Michael was 46, technical advances made it possible to restore vision in his right eye. As soon as the bandages were removed, he could see his wife's blue eyes and blond hair. But even 3 years later, he could not recognize her face unless she spoke to him, or recognize three-dimensional objects like a cube or a sphere unless they were moving. Of course Michael could still ski, but he found that he had to close his eyes to avoid falling over. On the slopes, seeing was more distracting than helpful.

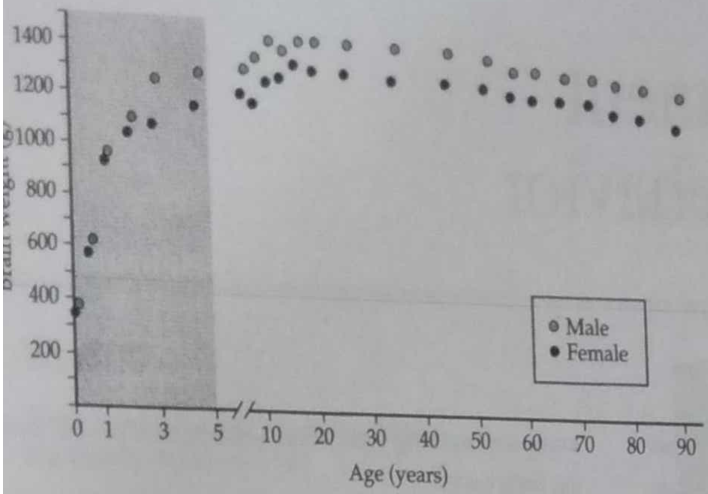
The doctors could tell that images were focusing properly on Michael's retina, so why was his vision so poor?

Age puts its stamp on the behavior of us all. Although the rate, progression, and orderliness of changes are especially prominent early in life, change is a feature of the entire life span. In this chapter we describe brains in terms of their progress through life from the womb to the tomb. The fertilization of an egg leads to a body with a brain that contains billions of neurons with an incredible number of connections. The pace of this process is extraordinary: during the height of prenatal growth of the human brain, more than 250,000 neurons are added per minute! We will describe the emergence of nerve cells, the formation of their connections, and the role of genes in shaping the nervous system. But we'll see that experience, gained through behavioral interactions with the environment, also sculpts the developing brain.

Growth and Development of the Brain Are Orderly Processes

Picture, if you can, the number of neurons in the mature human brain—about 100 billion. There are many types of neurons, each forming a vast array of hundreds or thousands of connections. The overall number of connections in the brain is about 100 trillion. Yet each of us began as a single microscopic cell—the fertilized egg. How can one cell divide and grow to form the most complicated machines on Earth, perhaps in the universe? Of course, some vital information was packed in the genes of that single cell, but we'll see that the developing nervous system also relies on its environment to guide the construction of this fabulous gadget between our ears.

One measure of brain development is weight, which reflects many developmental processes, especially those occurring during the first 5 years of life (**Figure 7.1**). Let's explore at the cellular level what happens in the developing brain.



7.1 Human Brain Weight as a Function of Age The age scale on this graph has been expanded for the first 5 years to show this period of rapid growth more clearly. (After Dekaban and Sadowsky, 1978.)

The brain emerges from the neural tube

A new human being begins when a sperm penetrates the wall of an egg cell. The fertilized egg, or **zygote**, has 46 chromosomes—23 from each parent—which contain genetic recipes for the development of a new individual. (A summary of the life cycle of cells, including a discussion of the basic genetic materials and how they direct cell activities, is provided in the appendix.) Within 12 hours after conception the single cell begins dividing, so after 3 days it has become a small mass of homogeneous cells, like a cluster of grapes, a mere 200 µm in diameter.

Within a week the emerging human embryo shows three distinct cell layers (**Figure 7.2a**). These layers are the beginnings of all the tissues of the embryo. The nervous system develops from the outer layer, called the **ectoderm** (from the Greek *ektos*, "out," and *derma*, "skin"). As the cell layers thicken, they grow into a flat oval plate. Uneven rates of cell division form a groove that will become the midline. At the head end of the groove, a thickened collection of cells forms 2 weeks after fertilization. Ridges of ectoderm continue to bulge on both sides of the middle position, forming the **neural groove** between them (**Figure 7.2*b***).

The pace of events then increases. The tops of the neural ridges come together to form the **neural tube** (**Figure 7.2*c***). At the anterior part of the neural tube, three subdivisions become apparent. These subdivisions correspond to the future **forebrain** (prosencephalon, consisting of the telencephalon and the diencephalon), **midbrain** (mesencephalon), and **hindbrain** (rhombencephalon, consisting of the metencephalon and the myelencephalon) (**Figure 7.2*d***), which were discussed in Chapter 2. The interior of the neural tube becomes the fluid-filled cerebral ventricles of the brain, the central canal of the spinal cord, and the passages that connect them.

By the end of the eighth week, the human embryo shows the rudimentary beginnings of most body organs. The rapid development of the brain is reflected in the fact that by this time the head is one-half the total size of the embryo. (Note that the developing human is called an **embryo** during the first 10 weeks after fertilization; thereafter it is called a **fetus**.) **Figure 7.2e** shows the prenatal development of the human brain from weeks 10 through 41. Even after this period, there are dramatic local changes as some brain regions grow more than others, well into the teenage years (P. M. Thompson et al., 2000).

Development of the Nervous System Can Be Divided into Six Distinct Stages

From a cellular viewpoint it is useful to consider brain development as a sequence of distinct stages, most of which occur during prenatal life:

1. *Neurogenesis*, the mitotic division of nonneuronal cells to produce neurons
2. *Cell migration*, the massive movements of nerve cells or their precursors to establish distinct nerve cell populations (nuclei in the CNS, layers of the cerebral cortex, and so on)
3. *Differentiation* of cells into distinctive types of neurons or glial cells
4. *Synaptogenesis*, the establishment of synaptic connections as axons and dendrites grow
5. *Neuronal cell death*, the selective death of many nerve cells
6. *Synapse rearrangement*, the loss of some synapses and development of others, to refine synaptic connections

zygote The fertilized egg.

ectoderm The outer cellular layer of the developing fetus, giving rise to the skin and the nervous system.

neural groove In the developing embryo, the groove between the neural folds.

neural tube An embryonic structure with subdivisions that correspond to the future forebrain, midbrain, and hindbrain.

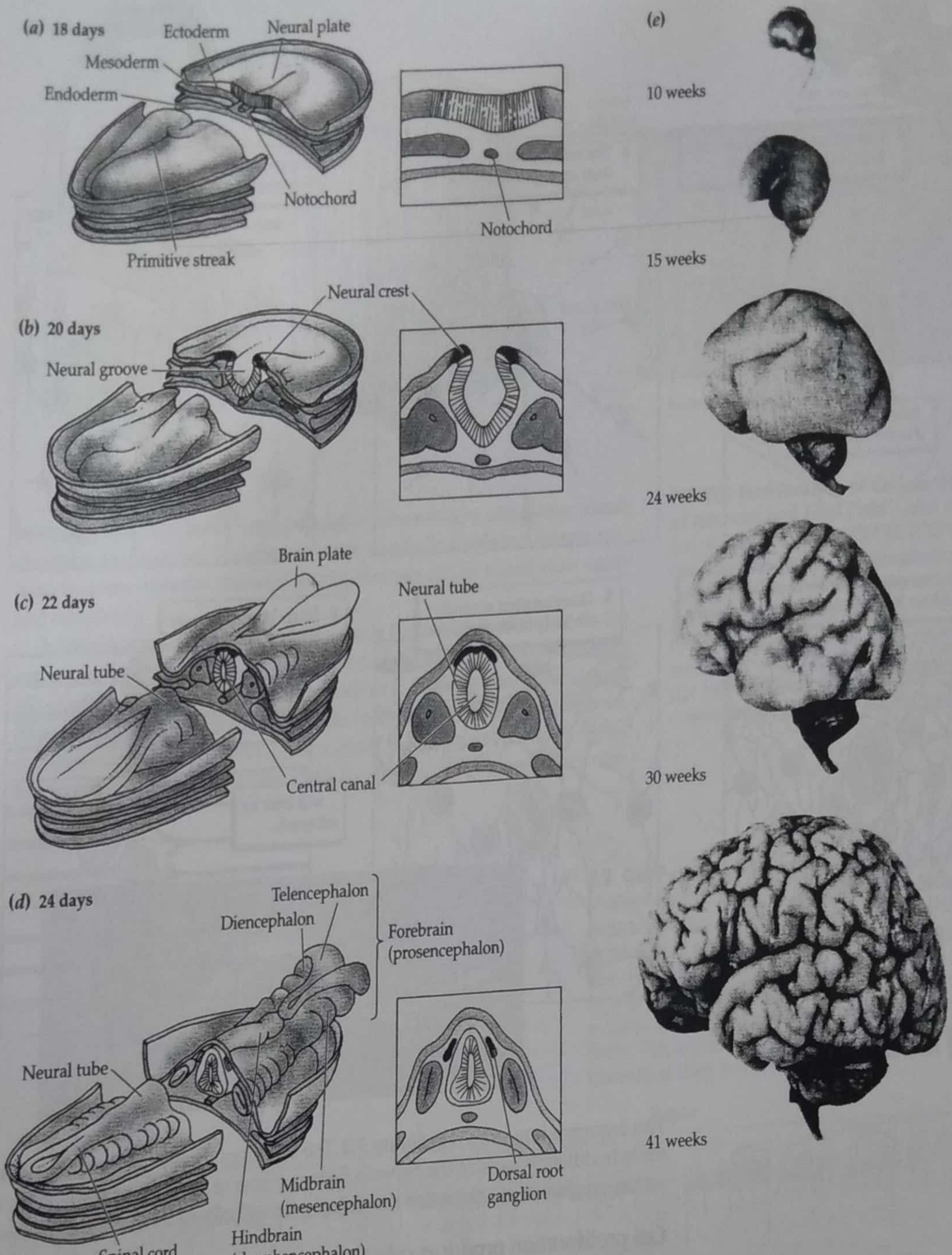
forebrain Also called *prosencephalon*. The frontal division of the neural tube, containing the cerebral hemispheres, the thalamus, and the hypothalamus.

midbrain Also called *mesencephalon*. The middle division of the brain.

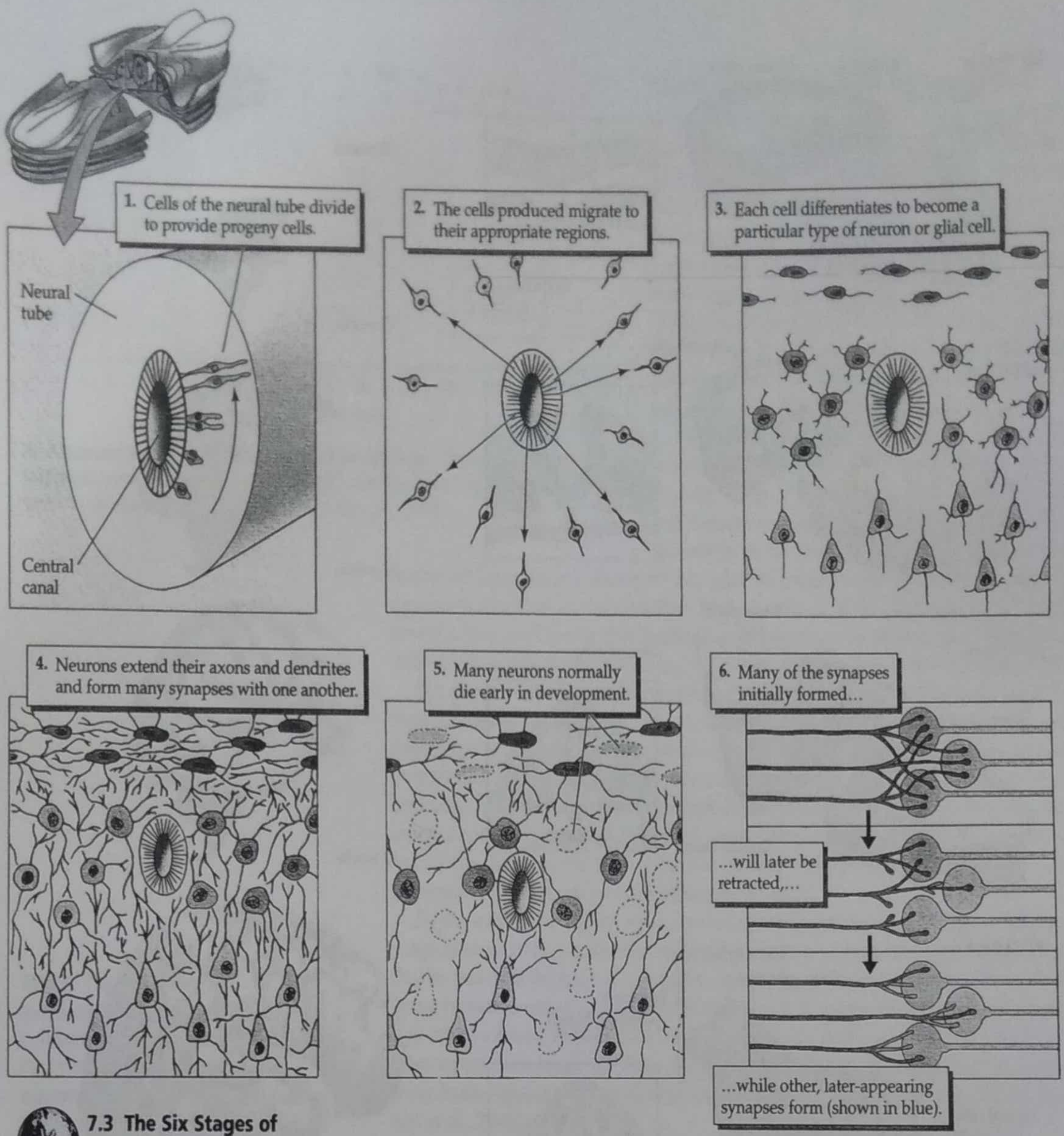
hindbrain Also called *rhombencephalon*. The rear division of the brain; in the mature vertebrate, the hindbrain contains the cerebellum, pons, and medulla.

embryo The earliest stage in a developing animal.

fetus A developing individual after the embryo stage.


(a) 18 days
Ectoderm
Neural plate
Mesoderm
Endoderm
Notochord
Notochord
Primitive streak
(b) 20 days
Neural crest
Neural groove
(c) 22 days
Brain plate
Neural tube
Neural tube
Central canal
(d) 24 days
Telencephalon
Diencephalon
Forebrain (prosencephalon)
Neural tube
Midbrain (mesencephalon)
Hindbrain (rhombencephalon)
Spinal cord
Dorsal root ganglion
(e)
10 weeks
15 weeks
24 weeks
30 weeks
41 weeks

7.2 Development of the Nervous System in the Human Embryo and Fetus (a) At 18 days the embryo has begun to implant in the uterine wall and consists of three layers of cells: endoderm, mesoderm, and ectoderm. A thickening of the ectoderm leads to the development of the neural plate (insets). (b) At 20 days the neural groove begins to develop. (c) At 22 days the neural groove has closed to form the neural tube with the rudimentary beginning of the brain at the anterior end. (d) A few days later, three major divisions of the brain—forebrain (prosencephalon, consisting of the telencephalon and diencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon)—are discernible. (e) In these lateral views of the human brain (shown at one-third size) at several stages of fetal development, note the gradual emergence of gyri and sulci. (Part e from Larroche, 1977.)


1. Cells of the neural tube divide to provide progeny cells.
Neural tube
Central canal
2. The cells produced migrate to their appropriate regions.
3. Each cell differentiates to become a particular type of neuron or glial cell.
4. Neurons extend their axons and dendrites and form many synapses with one another.
5. Many neurons normally die early in development.
6. Many of the synapses initially formed…
…will later be retracted,…
…while other, later-appearing synapses form (shown in blue).

7.3 The Six Stages of Neural Development

This sequence is portrayed in **Figure 7.3**. The six stages proceed at different rates and times in different parts of the nervous system. Some of the stages may overlap even within a region. In the discussion that follows, we will take up each stage in succession.

Cell proliferation produces cells that become neurons or glial cells

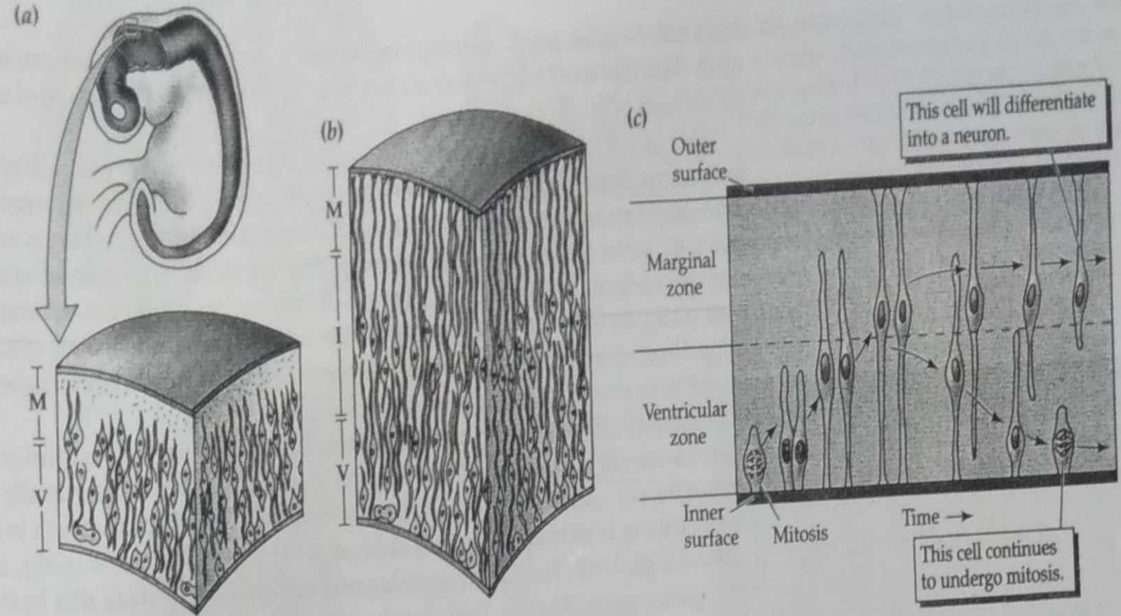
The production of nerve cells is called **neurogenesis**. Nerve cells themselves do not divide, but the cells that will give rise to neurons begin as a single layer of cells along the inner surface of the neural tube. These cells divide (in a process called **mitosis**) and gradually form a closely packed layer of cells called the **ventricular zone** (**Figure 7.4**). All neurons and glial cells are derived from cells that originate from such ventricular mitosis. Eventually some cells leave the ventricular zone and begin transforming into either a neuron or a glial cell. These two types of cells separate early in the ventricular zone.

Each part of an animal's brain has a species-characteristic "birth date." That is, there is an orderly chronological program for brain development, and it is possible to state the approximate days during development when particular cell groups stop dividing. Of course, given the complexity of vertebrate brains, it is difficult to trace individual cell de-

neurogenesis The mitotic division of nonneuronal cells to produce neurons.

mitosis The process of division of somatic cells that involves duplication of DNA.

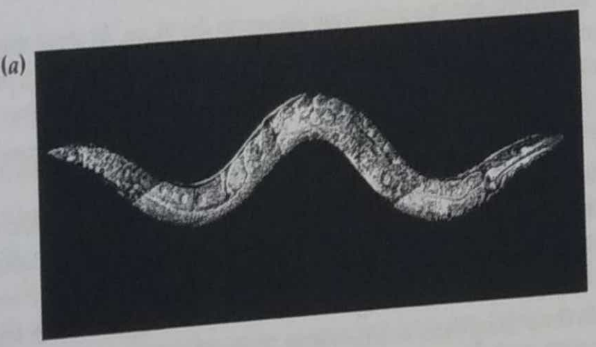
ventricular zone Also called *ependymal layer*. A region lining the cerebral ventricles that displays mitosis, providing neurons early in development and glial cells throughout life.


(a)
M
V
(b)
M
I
V
(c)
Outer surface
Marginal zone
Ventricular zone
Inner surface
Mitosis
Time →
This cell will differentiate into a neuron.
This cell continues to undergo mitosis.

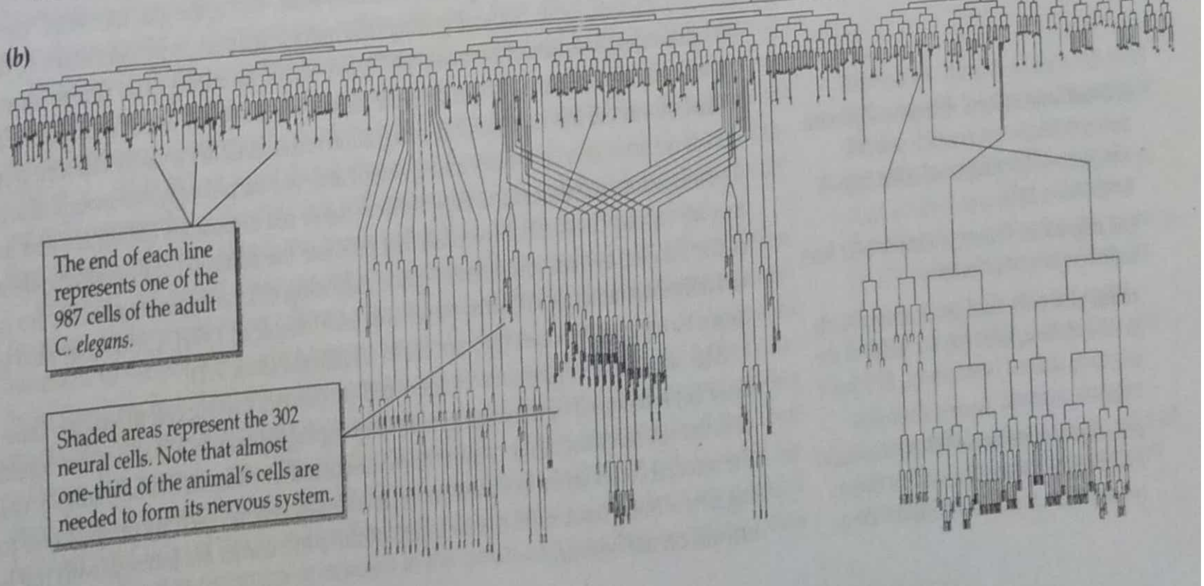
7.4 The Proliferation of Cellular Precursors of Neurons and Glial Cells (a) In this small section of the wall of the neural tube at an early stage of embryonic development, only ventricular (V) and marginal (M) layers are visible. (b) Later an intermediate (I) layer develops as the wall thickens. (c) Nuclei (within their cells) migrate from the ventricular layer to the outer layers. Some cells, however, return to the ventricular zone and divide, and the resulting daughter cells migrate to the outer layers, repeating the cycle.

velopment from the initial small population of ventricular cells. Descendants disappear in the crowd. However, in some simpler invertebrate nervous systems that have very few neurons, mitotic lineages can be traced more easily and completely.

A favorite animal of researchers who study the lineage of nerve cells is the nematode *Caenorhabditis elegans*, a tiny worm with fewer than a thousand cells, 302 of which are neurons. Because the body of *C. elegans* is almost transparent (**Figure 7.5a**), researchers have been able to trace the origins of each neuron, and they have identified several of the genes that control the worm's neural development (Wolinsky and Way, 1990). By observing the successive cell divi-



7.5 Cell Fate in a Simple Organism (a) This montage of photomicrographs shows the transparent body of *Caenorhabditis elegans*. (b) In this mitotic lineage of cells that give rise to the body of the adult *C. elegans*, nervous system cells are highlighted in blue. The structure and function of every cell can be predicted from its mitotic lineage. Such mitotic determination of cell differentiation does not seem important to the development of vertebrates. (Part a courtesy of Paola Dal Santo and Erik M. Jorgensen, University of Utah; *b* after Pines, 1992.)


(b)
Zygote
The end of each line represents one of the 987 cells of the adult C. elegans.
Shaded areas represent the 302 neural cells. Note that almost one-third of the animal's cells are needed to form its nervous system.

sions of a C. *elegans* zygote, investigators can exactly predict the fate of each cell in the adult—whether it will be a sensory neuron, muscle cell, skin cell, or other type of cell—on the basis of its mitotic "ancestors."

Whereas cell fate in C. *elegans* is a highly determined and stereotypical result of mitotic lineage (**Figure 7.5*b***), in vertebrates the paths that cells take to form the completed nervous system are more complex. Anatomical and genetic studies show that, in vertebrates, the paths of development include more-local regulatory mechanisms. The hallmark of vertebrate development is that cells sort themselves out via **cell–cell interactions**, taking on fates that are appropriate in the context of what neighboring cells are doing. Thus, vertebrate development is less hardwired and more susceptible to being shaped by environmental signals and, as we'll see, experience.

Traditionally, investigators of nervous system development have believed that most mammals have at birth all the neurons they will ever have. Researchers have usually attributed the postnatal increase of human brain weight (see Figure 7.1) to growth in the size of neurons, branching of dendrites, elaboration of synapses, increase in myelin, and addition of glial cells. But early reports that new neurons are added just after birth in some brain regions (Altman, 1969) have been supplemented with findings that new neurons are added even in adulthood in humans (Eriksson et al., 1998) and other animals (E. Gould, Reeves, et al., 1999; Magavi et al., 2000; Shingo et al., 2003). Likewise, nerve cells of the olfactory organ (which we use to detect odors) can be replaced throughout life (Sawamoto et al., 2006). Neurons are also added to the adult nervous system in songbirds (discussed in Chapters 12 and 19).

Elizabeth Gould and colleagues have found that enriched experience, such as learning, increases the rate of neurogenesis in adult mammals (E. Gould, Beylin, et al., 1999). So by studying this chapter, you may be giving your brain a few more neurons to use on exam day! Physical exercise also boosts neurogenesis in rats, an effect that can be blocked by stresses such as social isolation (Stranahan et al., 2006), so invest in exercise and a network of friends too.

New nerve cells migrate

Neurons of the developing nervous system are always on the move. At some stage the cells that form in the ventricular layer through mitotic division move away, in a process known as **cell migration**. In primates, by the time of birth, almost all presumptive nerve cells have completed their migration, but in rats, cells that will become neurons continue to migrate in some regions for several weeks following birth.

Cells do not move in an aimless, haphazard manner. Cells in the developing brain move along the surface of a particular type of glial cell (Rakic, 1985). Like spokes (radii) of a wheel, these **radial glial cells** extend from the inner to the outer surfaces of the emerging nervous system (**Figure 7.6**). The radial glial cells act as a series of guide wires, and the newly formed cells creep along them, as if they were "riding the glial monorail" (see Figure 7.6*c*) (Hatten, 1990). Some migrating cells move in a direction perpendicular to the radial glial cells (S. A. Anderson et al., 1997), like Tarzan swinging from vine to vine; others move in a rostral stream to produce the olfactory bulbs (C. M. Smith and Luskin, 1998).

Failures in the mechanism of cell migration result in either a vastly reduced population of neurons or a disorderly arrangement and, not surprisingly, behavioral disorders. The migration of cells and the outgrowth of nerve cell extensions (dendrites and axons) involve various chemicals. Molecules that promote the adhesion of developing elements of the nervous system, and thereby guide migrating cells and growing axons, are called **cell adhesion molecules** (**CAMs**) (Reichardt and Tomaselli, 1991). CAMs may also guide axons to regenerate when they are cut in adulthood (**Box 7.1**).

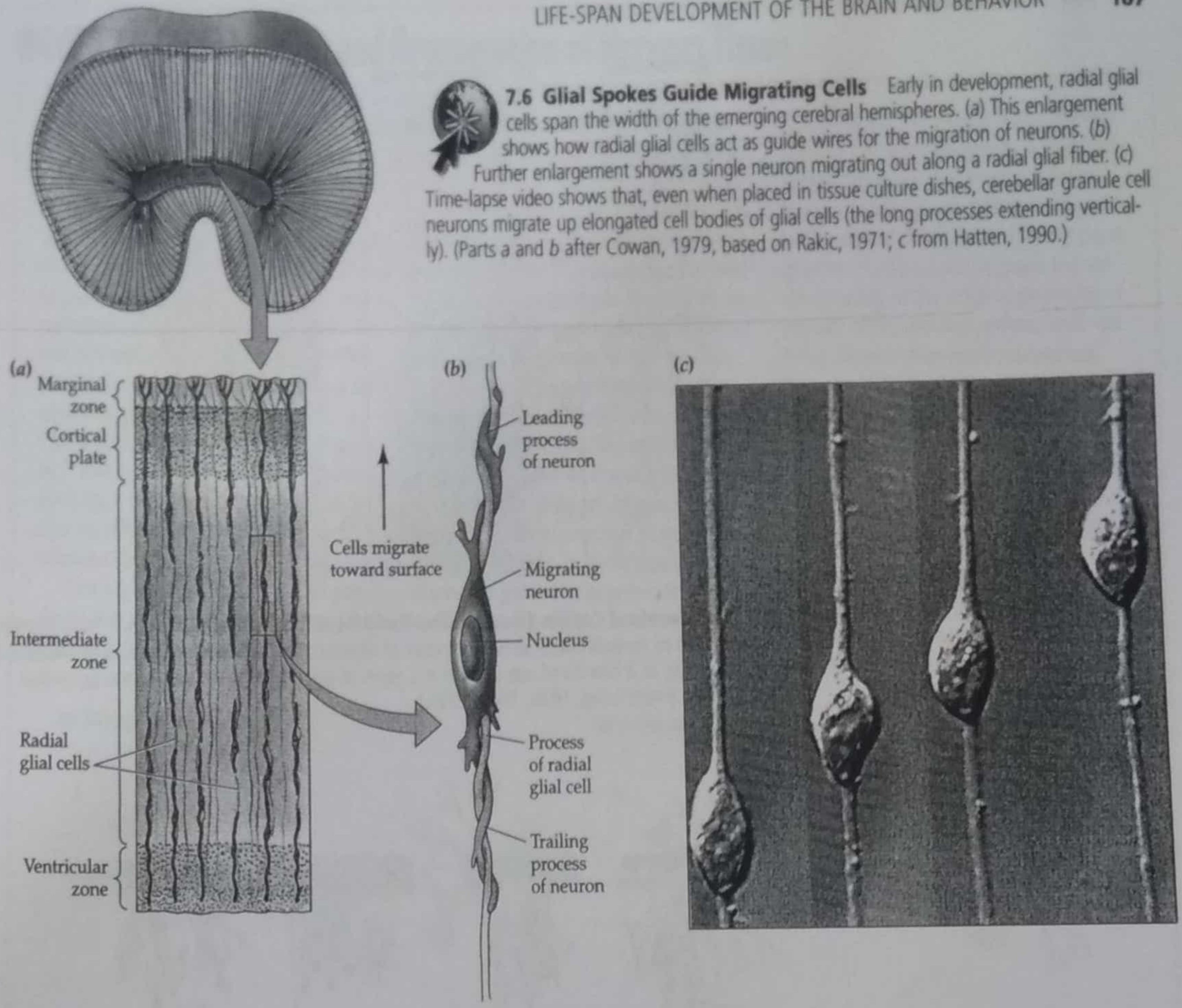
The single-file appearance of nerve cell precursors during cell migration (see Figure 7.6*a*) is followed by the aggregation, or grouping, of cells in a manner that foreshadows the nuclei of the adult brain that we discussed in Chapter 2. For example, cells of the cerebral cortex arrive in waves during fetal development, each successive wave forming a new outer layer, until the six layers of the adult cortex are formed, with the latest arrivals on the outside.

cell–cell interactions The general process during development in which one cell affects the differentiation of other, usually neighboring, cells.

cell migration The movement of cells from site of origin to final location.

radial glial cells Glial cells that form early in development, spanning the width of the emerging cerebral hemispheres, and guide migrating neurons.

cell adhesion molecule (CAM) A protein found on the surface of a cell that guides cell migration and/or axonal pathfinding.



7.6 Glial Spokes Guide Migrating Cells Early in development, radial glial cells span the width of the emerging cerebral hemispheres. (a) This enlargement shows how radial glial cells act as guide wires for the migration of neurons. (b) Further enlargement shows a single neuron migrating out along a radial glial fiber. (c) Time-lapse video shows that, even when placed in tissue culture dishes, cerebellar granule cell neurons migrate up elongated cell bodies of glial cells (the long processes extending vertically). (Parts a and b after Cowan, 1979, based on Rakic, 1971; c from Hatten, 1990.)

Cells in newly formed brain regions differentiate into neurons

Newly arrived cells in the brain bear no more resemblance to mature nerve cells than they do to the cells of other organs. Once they reach their destinations, however, the cells begin to use, or **express**, particular genes. This means that the cell transcribes a particular subset of genes to make the particular proteins it needs. This process of **cell differentiation** allows the cell to acquire the distinctive appearance and functions of neurons characteristic of that particular region (**Figure 7.7**).

What controls differentiation is not completely understood, but two classes of influence are known. First, intrinsic self-organization is an important factor; cerebellar Purkinje cells develop a very specific dendritic tree (**Figure 7.8**)—even **in vitro** (in a glass dish) (Seil et al., 1974). When a cell shows characteristics that are independent of neighboring cells, we say that it is acting in a **cell-autonomous** manner. In cell-autonomous differentiation, presumably only the genes within that cell are directing events.

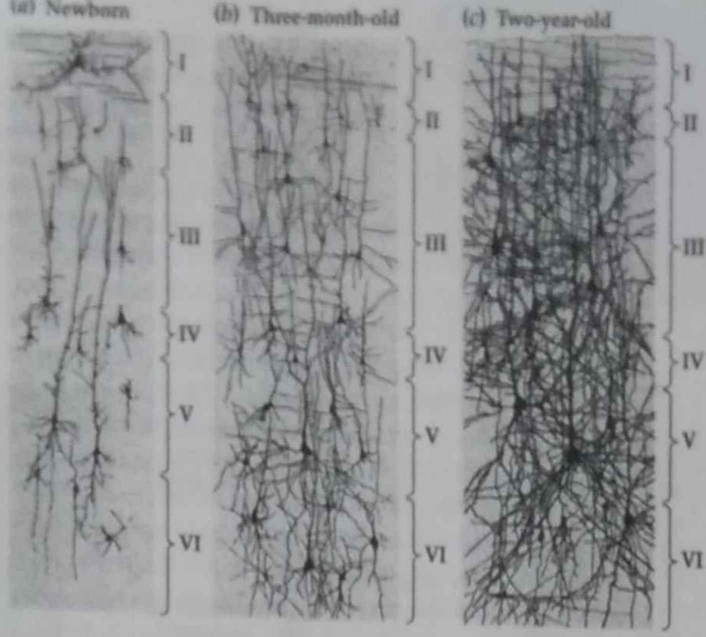
However, the neural environment also greatly influences nerve cell differentiation. In other words, neighboring cells are a second major influence on the differentiation of neurons. In vertebrates (unlike the nematode *C. elegans*), young neural cells seem to have the capacity to become many varieties of neurons, and the particular type of neuron that a cell becomes depends on where it happens to be and what its neighboring cells are. For example, consider spinal motoneurons—cells in the spinal cord that send their axons out to control muscles. Motoneurons are large, multipolar cells found in the left and right sides of the spinal cord in the ventral horn of gray matter. Motoneurons are among the first recognizable neurons in the spinal cord, and they send their axons

expression The process by which a cell makes an mRNA transcript of a particular gene.

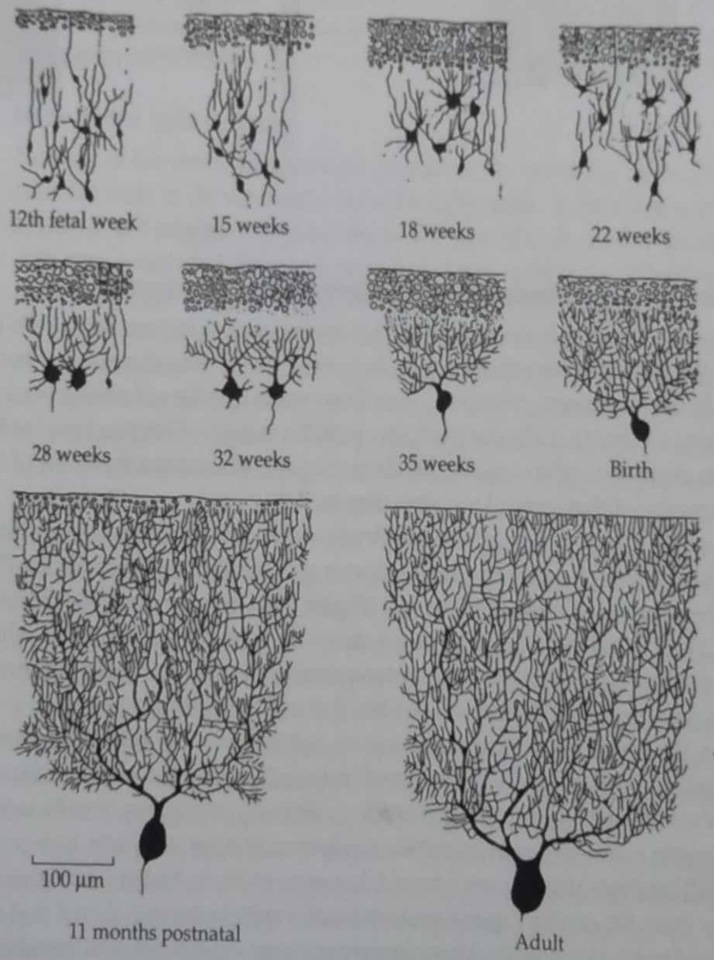
cell differentiation The developmental stage in which cells acquire distinctive characteristics, such as those of neurons, as the result of expressing particular genes.

in vitro Literally "in glass" (in Latin). Usually, in a laboratory dish; outside the body.

cell-autonomous Referring to cell processes that are directed by the cell itself rather than being under the influence of other cells.


(a) Newborn
(b) Three-month-old
(c) Two-year-old
I
II
III
IV
V
VI
I
II
III
IV
V
VI
I
II
III
IV
V
VI

7.7 Cerebral Cortex Tissue in the Early Development of Humans These representations of cerebral cortex show the extent of neural connections and neuronal differentiation at birth (*a*), at 3 months of age (*b*), and at 2 years of age (*c*). Numerals refer to the six cortical layers. (From Conel, 1939, 1947, 1959.)


12th fetal week
15 weeks
18 weeks
22 weeks
28 weeks
32 weeks
35 weeks
Birth
100 μm
11 months postnatal
Adult

7.8 The Development of Purkinje Cells in the Human Cerebellum (After Zecevic and Rakic, 1976.)

BOX 7.1 Degeneration and Regeneration of Nervous Tissue

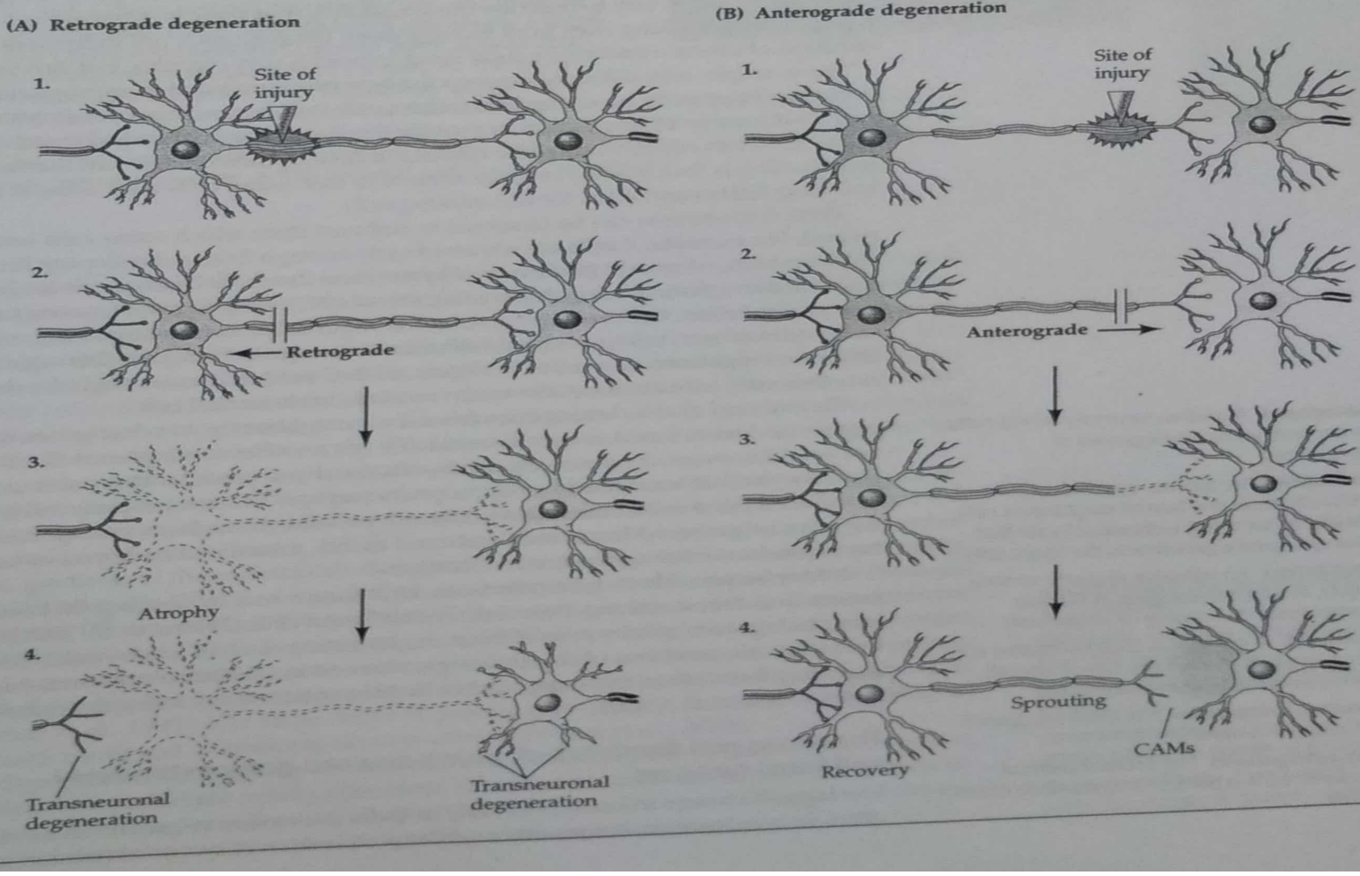
When a mature nerve cell is injured, it can regrow in several ways. Complete replacement of injured nerve cells is rare in mammals, but Figures A and B illustrate two characteristic forms of degeneration and regeneration in the mammalian peripheral and central nervous systems. Injury close to the cell body of a neuron produces a series of changes resulting in the eventual destruction of the cell; this process is called **retrograde degeneration** (Figure A, 2 and 3). If the injured neuron dies, the target cells formerly innervated by that neuron may show signs of *transneuronal degeneration* (Figure A, 4).

Cutting through the axon also produces loss of the distal part of the axon (the part that is separated from the cell body). This process is called *Wallerian degeneration*, or **anterograde degeneration** (Figure B, 2 and 3). The part of the axon that remains connected to the cell body may regrow. Severed axons in the peripheral nervous system regrow readily. Sprouts emerge from the part of the axon that is still connected to the nerve cell body and advance slowly toward the periphery (Figure B, 4). Cell adhesion molecules (CAMs) help guide the regenerating axons. Some fishes and amphibians have an enviable advantage over humans: after an injury to the brain they can regenerate many of the lost connections. In these cases, CAMs appear to guide the regeneration (as we'll see in Box 7.2).

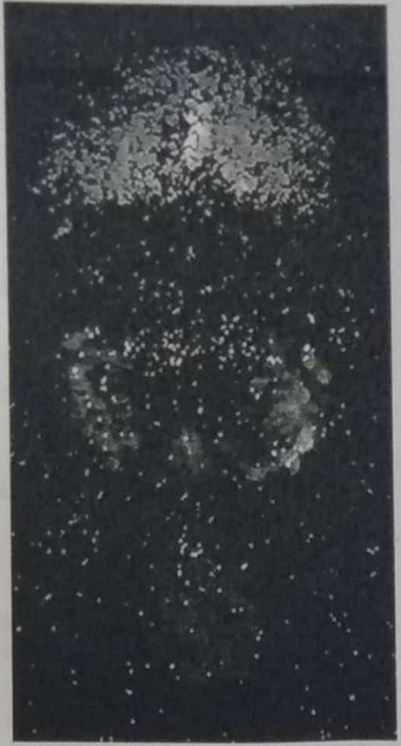
One interesting thing about regeneration of the nervous system is that it involves processes that seem similar to those that take place during an organism's original development. Studying regeneration, then, may increase our understanding of the original processes of growth of the nervous system, and vice versa. From a therapeutic viewpoint, these studies may help scientists learn how to induce repair and regrowth of damaged neural tissue in humans.

retrograde degeneration Destruction of the nerve cell body following injury to its axon.

anterograde degeneration Also called *Wallerian degeneration*. The loss of the distal portion of an axon resulting from injury to the axon.


(A) Retrograde degeneration

(B) Anterograde degeneration



7.9 The Induction of Spinal Motoneurons Spinal motoneurons normally cluster in the ventral region on either side of the spinal cord. In this cross section of embryonic chick spinal cord, the notochord (green circle at bottom) lies just beneath the spinal cord and secretes a protein called Sonic hedgehog. The concentration of this protein in the ventral spinal cord induces the cells there to develop as motoneurons (gold). Another protein (blue) is expressed only in the dorsal spinal cord. (Courtesy of Thomas Jessell.)

out early in fetal development. How do these cells "know" they should express motoneuron-specific genes and differentiate into motoneurons?

Examination of the late divisions giving rise to motoneurons makes it clear that the cells are not attending to mitotic lineage (Leber et al., 1990). Instead, some spinal cells are directed to become motoneurons under the influence of other cells lying just ventral to the developing spinal cord—in the **notochord**, a rodlike structure that forms along the midline (see Figure 7.2*a*) (Roelink et al., 1994). The notochord releases a protein (playfully named Sonic hedgehog) that diffuses to the spinal cord and directs some (but not all) cells to become motoneurons (**Figure 7.9**).

The influence of one set of cells on the fate of neighboring cells is known as **induction**; the notochord induces some spinal cord cells to differentiate into motoneurons. Induction of this sort has been demonstrated many times in the developing vertebrate body and brain. Another way to describe the situation is that there is extensive cell–cell interaction, each cell taking cues from its neighbors. Because each cell influences the differentiation of others, vertebrate neural development is very complex, but also very flexible.

For example, cells differentiate into the type of neuron that is appropriate for wherever they happen to be in the brain; thus, cell–cell interaction coordinates development—directing differentiation to provide the right type of neuron for each part of the brain. Another consequence of the reliance of development on cell–cell interactions such as induction is that, if a few cells are injured or lost, other cells will "answer the call" of inducing factors and fill in for the missing cells.

This phenomenon can be observed in embryos from which some cells have been removed. For example, if cells are removed early enough from a developing limb bud in a chick embryo, other cells pitch in, and by the time the chick hatches, the limb looks normal—with no parts missing. Embryologists refer to such adaptive responses to early injury as **regulation**: the developing animal compensates for missing or injured cells. Because cell fate is so tightly coupled with mitotic lineage in *C. elegans*, this organism shows little or no regulation. If a cell in *C. elegans* is killed (with a laser through the microscope), no other cells take its place; the worm must do without that cell.

This system of cells taking cues from their neighbors as to what genes they should express and what function they should fulfill has another consequence: if cells that have not yet differentiated extensively can be obtained and placed into a particular brain region, they will differentiate in an appropriate way and become properly integrated. Such undifferentiated cells, called **stem cells**, are present throughout embryonic tissues, so they can be gathered from umbilical-cord blood, miscarried embryos, or unused embryos produced during in vitro fertilization.

It may be possible to take cells from adult tissue and, by treating them with various factors in a dish, transform them into "adult" stem cells (Palmer et al., 2001). It is hoped that placing stem cells in areas of brain degeneration, such as loss of myelination in multiple sclerosis, or of loss of dopaminergic neurons in Parkinson's disease, might reverse such degeneration as the implanted cells differentiate to fill in for the missing components (S. Liu et al., 2000).

The axons and dendrites of young neurons grow extensively and form synapses

The biggest change in brain cells early in life is the extensive growth of axons and dendrites (termed **process outgrowth**) and the proliferation of synapses (termed **synaptogen-**

notochord A midline structure arising early in the embryonic development of vertebrates.

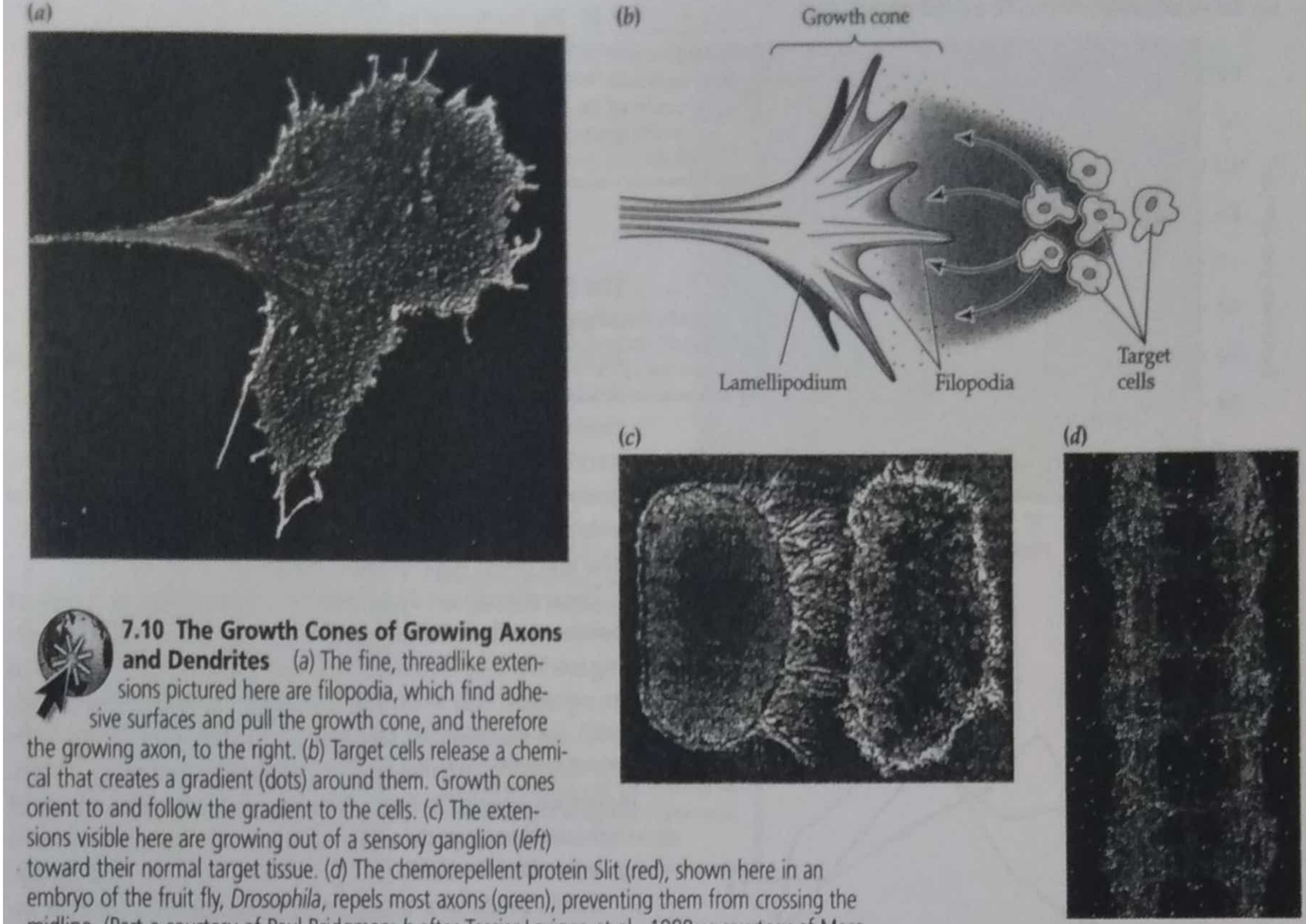
induction The process by which one set of cells influences the fate of neighboring cells, usually by secreting a chemical factor that changes gene expression in the target cells.

regulation An adaptive response to early injury, as when developing individuals compensate for missing or injured cells.

stem cell A cell that is undifferentiated and therefore can take on the fate of any cell that a donor organism can produce.

process outgrowth The extensive growth of axons and dendrites.

synaptogenesis The establishment of synaptic connections as axons and dendrites grow.



7.10 The Growth Cones of Growing Axons and Dendrites (a) The fine, threadlike extensions pictured here are filopodia, which find adhesive surfaces and pull the growth cone, and therefore the growing axon, to the right. (b) Target cells release a chemical that creates a gradient (dots) around them. Growth cones orient to and follow the gradient to the cells. (c) The extensions visible here are growing out of a sensory ganglion (*left*) toward their normal target tissue. (d) The chemorepellent protein Slit (red), shown here in an embryo of the fruit fly, *Drosophila*, repels most axons (green), preventing them from crossing the midline. (Part *a* courtesy of Paul Bridgman; *b* after Tessier-Lavigne et al., 1988; *c* courtesy of Marc Tessier-Lavigne; *d* courtesy of Julie Simpson and Corey S. Goodman.)

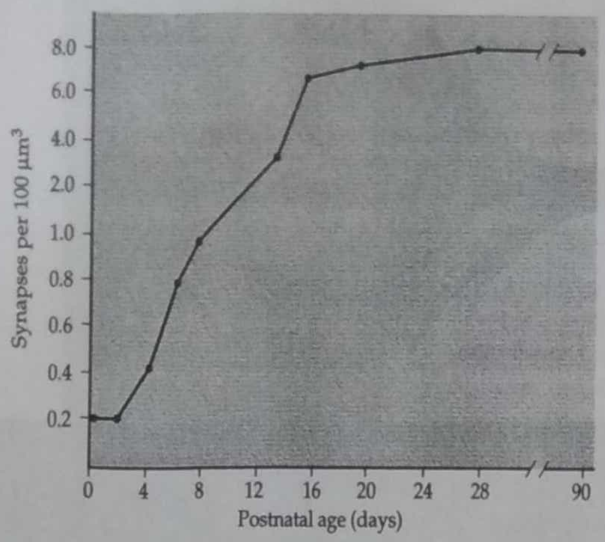
esis). At the tips of both axons and dendrites are **growth cones**, swollen ends from which extensions emerge (**Figure 7.10*a* and *b***). The very fine outgrowths, called **filopodia** (singular *filopodium*, from the Latin *filum*, "thread," and the Greek *pous*, "foot"), are spikelike; the sheetlike extensions are called **lamellipodia** (singular *lamellipodium*, from a form of the Latin *lamina*, "thin plate"). Both the filopodia and the lamellipodia seem to adhere to the extracellular environment, and then they contract to pull the growth cone in a particular direction (the growing axon or dendrite follows behind it). Dendritic growth cones are found in adults, mediating the continued elongation and change in dendrites that occurs throughout life in response to experience.

What guides axons along the paths they take? Axons are guided by chemicals released by the target nerve cells or other tissues, such as muscles (C. S. Goodman, 1996; Tessier-Lavigne and Placzek, 1991). The axon growth cone responds to the concentration gradients of these chemicals that provide directional guidance, as illustrated in **Figure 7.10*b* and *c***. Chemical signals that attract certain growth cones are called **chemoattractants** (Hiramoto et al., 2000); chemicals that repel growth cones are **chemorepellents** (M. S. Chen et al., 2000; Keynes and Cook, 1992). For example, because it is important for some axons to remain on one side of the body and for others to cross over, a protein called Slit repels some axons to prevent them from crossing the midline (Figure 7.10*d*) (Brose et al., 1999). The same secreted protein may act as a chemoattractant to some growth cones and a chemorepellent to others (Polleux et al., 2000).

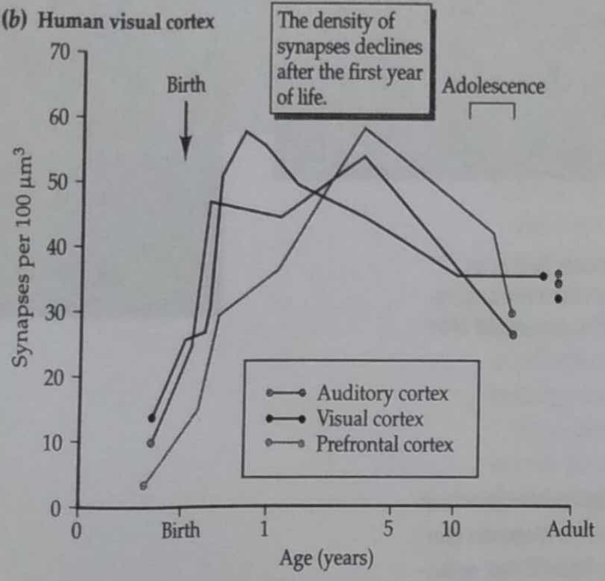
Synapses can form rapidly on dendrites and dendritic spines (**Figure 7.11**). The spines themselves proliferate rapidly after birth. These connections can be affected by postnatal experience, as we will see in Chapter 18. To support the metabolic needs of the expanded dendritic tree, the nerve cell body greatly increases in volume.

growth cone	The growing tip of an axon or a dendrite.
filopodia	Very fine, tubular outgrowths from the growth cone.
lamellipodia	Sheetlike extensions of a growth cone.
chemoattractants	Compounds that attract particular classes of growth cones.
chemorepellents	Compounds that repel particular classes of growth cones.

(*a*) Rat visual cortex



(*b*) Human visual cortex



7.11 The Postnatal Development of Synapses The rate of synapse development in the visual cortex of rats (a) and humans (*b*). In humans, note the decline in the density of synapses after the first year of life. (Part a after Blue and Parnavelas, 1983; *b* from Huttenlocher et al., 1982.)

The death of many neurons is a normal part of development

As strange as it may seem, cell death is a crucial phase of brain development, especially during embryonic stages. This developmental stage is not unique to the nervous system. Naturally occurring **cell death**, also called **apoptosis** (from the Greek *apo*, "away from," and *ptosis*, "act of falling"), is evident as a kind of sculpting process in the emergence of other tissues in both animals and plants (Oppenheim, 1991).

These cells are not dying because of a defect. Rather, it appears that these cells have "decided" to die and are actively committing suicide. Your chromosomes carry **death genes**—genes that are expressed only when a cell undergoes apoptosis (Peter et al., 1997). For example, the **caspases** are a family of proteases (protein-dissolving enzymes) that cut up proteins and nuclear DNA. Apoptosis appears to begin with a sudden influx and release of Ca^{2+} ions that cause the mitochondria inside the cell to release a protein called, devilishly enough, **Diablo** (Verhagen et al., 2000).

Diablo binds to a family of proteins, the well-named **inhibitors of apoptosis proteins (IAPs)** (Earnshaw et al., 1999). The IAPs, in turn, have been inhibiting the caspases. So when Diablo binds the IAPs, the caspases are free to dismantle the cell. **Bcl-2** proteins block apoptosis by preventing Diablo release from the mitochondria. This intricate system of checks and balances, which determines whether a cell gives up the ghost (**Figure 7.12**), must have been established long ago in evolution, since homologs of the genes that produce these proteins function similarly in *C. elegans*.

In the nervous system, the number of cells that die during early development is quite large. In some regions of the brain and spinal cord, *most* of the young nerve cells die during prenatal development. In 1958, Viktor Hamburger (1900–2001) first described naturally occurring neuronal cell death in chicks, in which nearly half the originally produced spinal motoneurons die before the chick hatches (**Figure 7.13a**). Genetically interfering with neural apoptosis in fetal mice causes them to grow brains that are too large to fit in the skull (Depaepe et al., 2005), so we can see how vital it is that some cells die.

Several factors influence this massive cell death in the nervous system. The extent of cell death is regulated in part by factors associated with the synaptic targets of cells. Reduction of the size of the synaptic target invariably reduces the number of surviving nerve cells. For example, if the leg of a tadpole is removed early in development, many more developing spinal motoneurons die than if the leg had remained in position. Conversely, grafting on an extra leg—a technique that is possible with chicken embryos and tadpoles—reduces the usual loss of cells; in such cases the mature spinal cord has more than the usual number of motoneurons on that side.

Neurons compete for connections to target structures (other nerve cells or end organs, such as muscle). Cells that make adequate synapses remain; those without a place to form synaptic connections die. Apparently the cells compete not just for synaptic sites, but for a chemical that the target structure makes and releases. Neurons that receive enough of the chemical survive; those that do not, die.

cell death or apoptosis The developmental process during which "surplus" cells die.

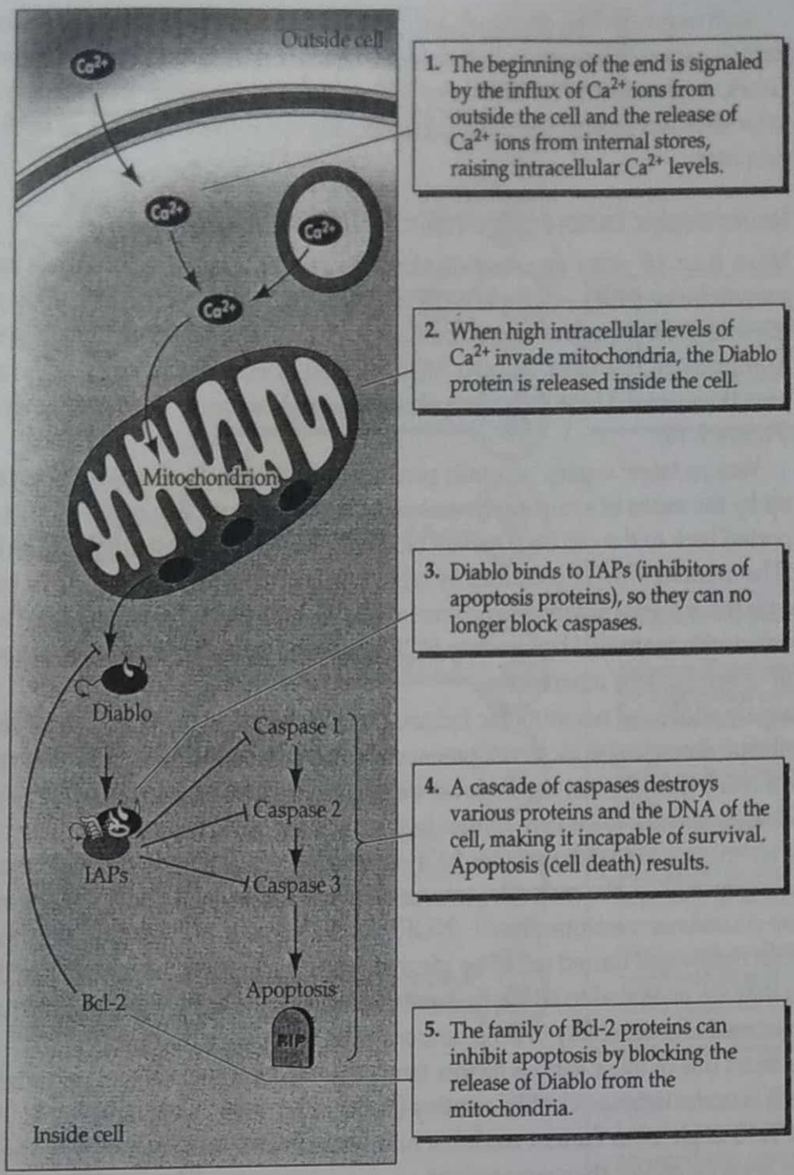
death gene A gene that is expressed only when a cell becomes committed to natural cell death (apoptosis).

caspases A family of proteins that regulate cell death (apoptosis).

Diablo A protein released by mitochondria, in response to high calcium levels, that activates apoptosis.

inhibitor of apoptosis proteins (IAPs) A family of proteins that inhibit caspases and thereby stave off apoptosis.

Bcl-2 A family of proteins that regulate apoptosis.


Outside cell
Ca2+
Ca2+
Ca2+
Ca2+
Mitochondrion
Diablo
Caspase 1
Caspase 2
Caspase 3
IAPs
Apoptosis
RIP
Bcl-2
Inside cell

1. The beginning of the end is signaled by the influx of Ca^{2+} ions from outside the cell and the release of Ca^{2+} ions from internal stores, raising intracellular Ca^{2+} levels.

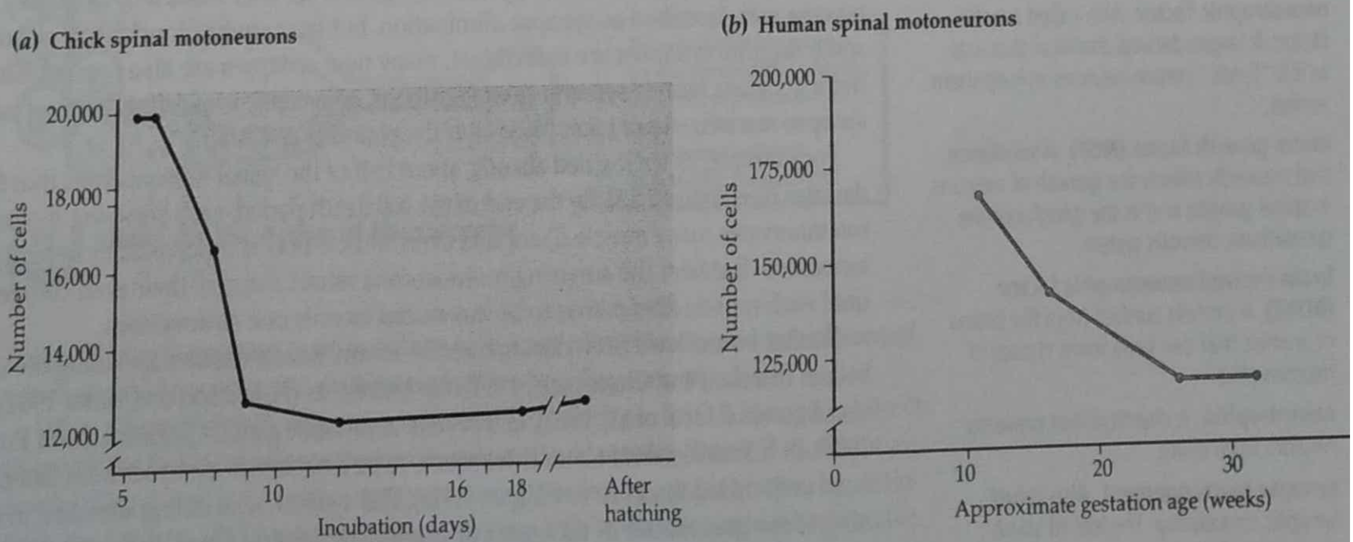
2. When high intracellular levels of Ca^{2+} invade mitochondria, the Diablo protein is released inside the cell.

3. Diablo binds to IAPs (inhibitors of apoptosis proteins), so they can no longer block caspases.

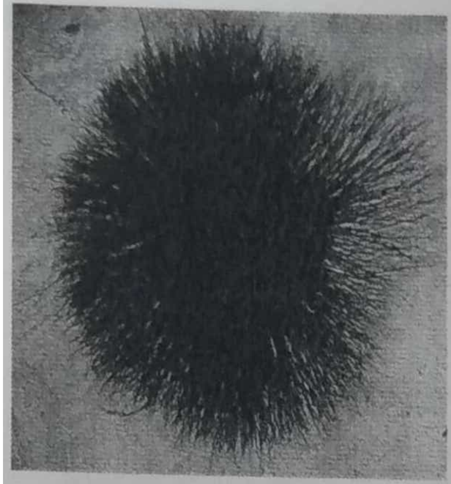
4. A cascade of caspases destroys various proteins and the DNA of the cell, making it incapable of survival. Apoptosis (cell death) results.

5. The family of Bcl-2 proteins can inhibit apoptosis by blocking the release of Diablo from the mitochondria.

7.12 Death Genes Regulate Apoptosis



7.13 Many Neurons Die during Normal Early Development The pattern of neuronal cell death in spinal motoneurons of chicks (*a*) and humans (*b*). Many neuronal populations show a similar pattern of apoptosis. (Part *a* from Hamburger, 1975; *b* from Forger and Breedlove, 1987.)



7.14 The Effects of Nerve Growth Factor If NGF is added to the solution bathing a spinal ganglion grown in vitro (in a glass dish), neuronal processes grow outward in an exuberant, radiating fashion. (From Levi-Montalcini, 1963.)

Such target-derived chemicals are called **neurotrophic factors** (or simply *trophic factors*) because they act as if they "feed" the neurons to help them survive (in Greek, *trophe* means "nourishment"). The neurotrophic factor that was the first to be identified prevents the death of developing sympathetic neurons, as we'll discuss next.

Neurotrophic factors allow neurons to survive and grow

More than 40 years ago, investigators discovered a substance—called **nerve growth factor (NGF)**—that markedly affects the growth of neurons in spinal ganglia and in the ganglia of the sympathetic nervous system (Levi-Montalcini, 1982). Administered to a chick embryo, NGF resulted in many more sympathetic neurons than usual. These cells were also larger and had more extensive processes (**Figure 7.14**).

Various target organs normally produce NGF during development. It is taken up by the axons of sympathetic neurons that innervate those organs and transported back to the cell body, where NGF prevents the sympathetic neurons from dying. The amount of NGF produced by targets during development is roughly correlated with the amount of sympathetic innervation that the targets receive in adulthood. Thus, cell death, controlled by access to NGF, provides each target with an appropriate amount of sympathetic innervation.

There are additional neurotrophic factors, each one affecting the survival of a particular cell type during a specific developmental period. One such factor, purified from the brains of many animals, was named **brain-derived neurotrophic factor (BDNF)**. The gene for BDNF turned out to be very similar to the gene for NGF. Investigators used molecular techniques to search for other NGF-related molecules and found several more.

The family of NGF-like molecules was named the **neurotrophin** family, and its members are numbered: neurotrophin-1 (NGF), -2 (BDNF), -3, and -4/5 (the fifth neurotrophin discovered turned out to be identical with the fourth—oops). Neurotrophic factors that are unrelated to NGF also have been found, including ciliary neurotrophic factor (named after its ability to keep neurons from ciliary ganglia alive in vitro).

The exact role of these various factors (and other neurotrophic factors yet to be discovered) is under intense scientific scrutiny (Kafitz et al., 1999; Lewin and Barde, 1996). **Figure 7.15** depicts our current model of how neurotrophic factors influence the survival of neurons and/or their connections.

Synaptic connections are refined by synapse rearrangement

Just as not all the neurons produced by a developing individual are kept into adulthood, some of the synapses formed early in development are later retracted. Originally this process was described as synapse elimination, but later studies found that, although some original synapses are indeed lost, many new synapses are also formed. Thus a more accurate term is **synapse rearrangement**, or *synaptic remodeling*. In most cases, synapse rearrangement takes place after the period of cell death.

For example, as we learned already, about half of the spinal motoneurons that form die later (see Figure 7.13). By the end of the cell death period, each surviving motoneuron innervates many muscle fibers, and every muscle fiber is innervated by several motoneurons. But later the surviving motoneurons retract many of their axon collaterals, until each muscle fiber comes to be innervated by only one motoneuron.

Similar events have been documented in several neural regions, including the cerebellum (Mariani and Changeaux, 1981), the brainstem (H. Jackson and Parks, 1982), the visual cortex (Hubel et al., 1977), and several autonomic ganglia (Lichtman and Purves, 1980). In human cerebral cortex there seems to be a net loss of synapses from late childhood until midadolescence (see Figure 7.11*b*). This synaptic remodeling is evident in thinning of the gray matter in the cortex as pruning of dendrites and axon terminals progresses. The thinning process continues in a caudal-rostral direction during maturation (**Figure 7.16**), so prefrontal cortex is affected last (Gogtay et al., 2004). Because prefrontal cortex is important for inhibiting behavior (see Chapter 19), it has been argued that this

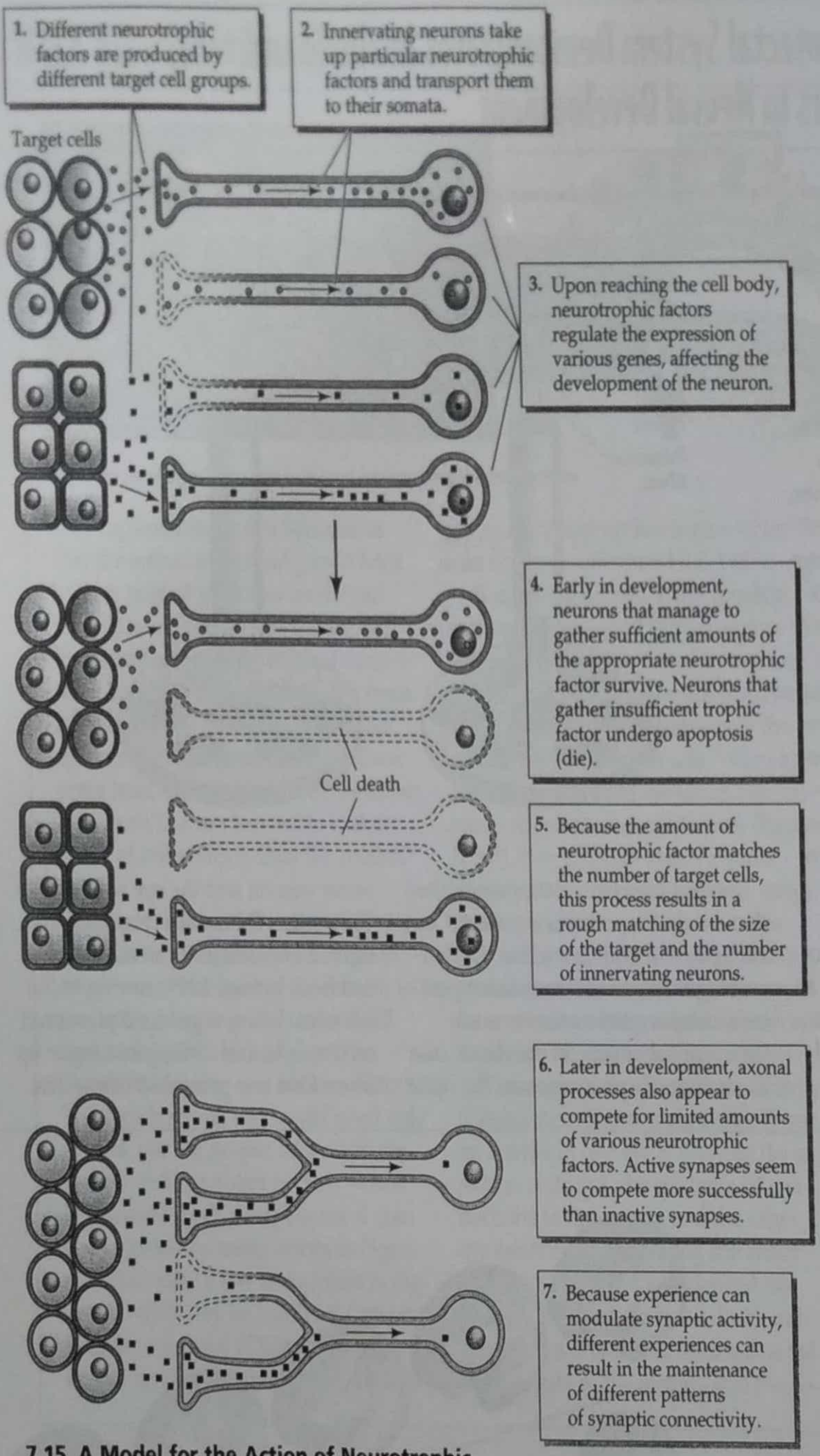
neurotrophic factor Also called *trophic factor*. A target-derived chemical that acts as if it "feeds" certain neurons to help them survive.

nerve growth factor (NGF) A substance that markedly affects the growth of neurons n spinal ganglia and in the ganglia of the ympathetic nervous system.

rain-derived neurotrophic factor BDNF) A protein purified from the brains f animals that can keep some classes of eurons alive.

eurotrophin A chemical that prevents eurons from dying.

ynapse rearrangement Also called *ynaptic remodeling*. The loss of some ynapses and the development of others; refinement of synaptic connections that often seen in development.

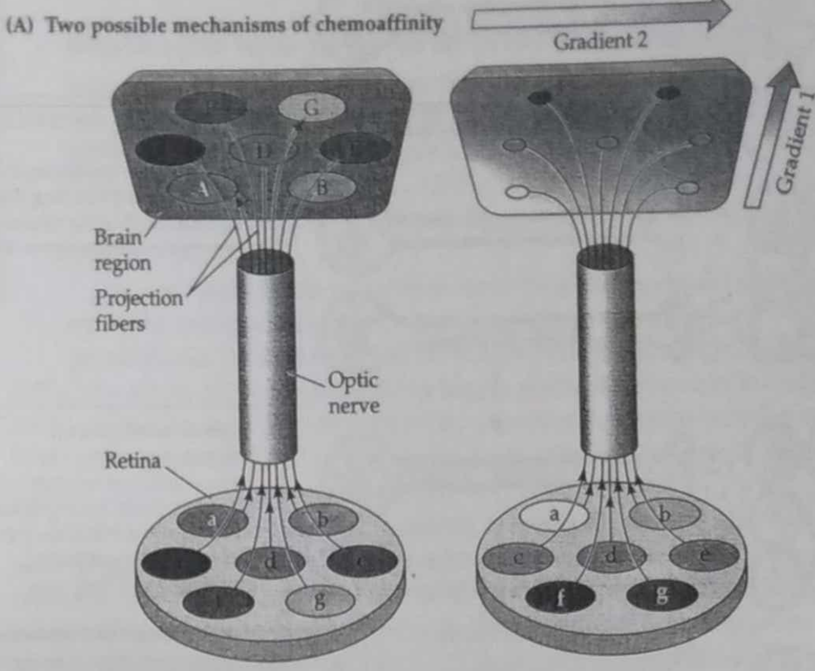

1. Different neurotrophic factors are produced by different target cell groups.
2. Innervating neurons take up particular neurotrophic factors and transport them to their somata.
Target cells
3. Upon reaching the cell body, neurotrophic factors regulate the expression of various genes, affecting the development of the neuron.
4. Early in development, neurons that manage to gather sufficient amounts of the appropriate neurotrophic factor survive. Neurons that gather insufficient trophic factor undergo apoptosis (die).
Cell death
5. Because the amount of neurotrophic factor matches the number of target cells, this process results in a rough matching of the size of the target and the number of innervating neurons.
6. Later in development, axonal processes also appear to compete for limited amounts of various neurotrophic factors. Active synapses seem to compete more successfully than inactive synapses.
7. Because experience can modulate synaptic activity, different experiences can result in the maintenance of different patterns of synaptic connectivity.

7.15 A Model for the Action of Neurotrophic Factors

delayed brain maturation may contribute to teenagers' impulsivity and lack of control, which should be considered a mitigating factor when they commit crimes.

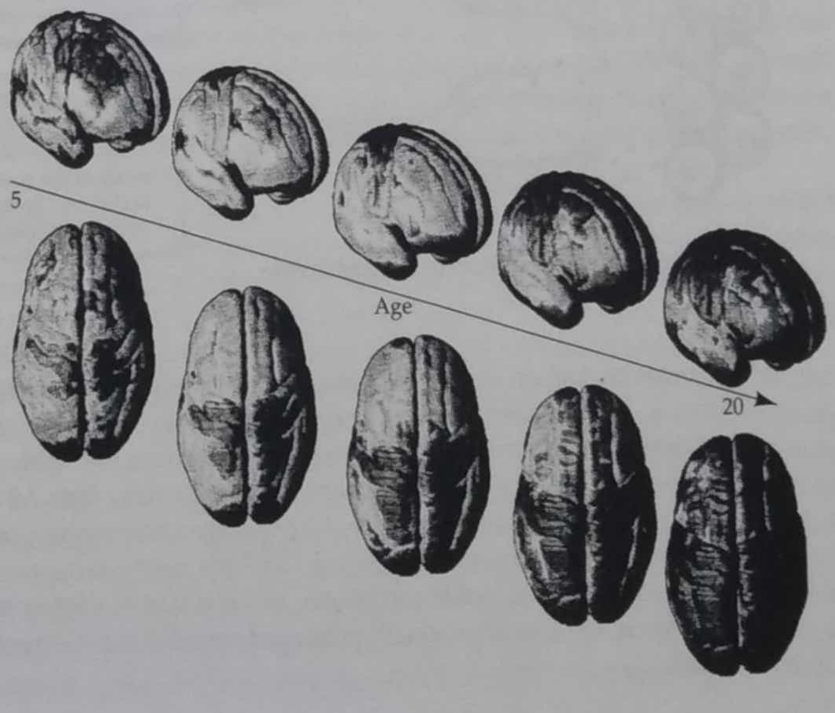
What determines which synapses are kept and which are lost? Although we don't know all the factors, one important influence is neural activity (**Box 7.2** shows an example). One theory is that active synapses take up some neurotrophic factor that maintains the synapse, while inactive synapses get too little trophic factor to remain stable. Intellectual stimulation probably contributes, as suggested by the fact that teenagers with the highest IQ show an especially prolonged period of cortical thinning (P. Shaw et al., 2006).

BOX 7.2 The Frog Retinotectal System Demonstrates Intrinsic and Extrinsic Factors in Neural Development


(A) Two possible mechanisms of chemoaffinity

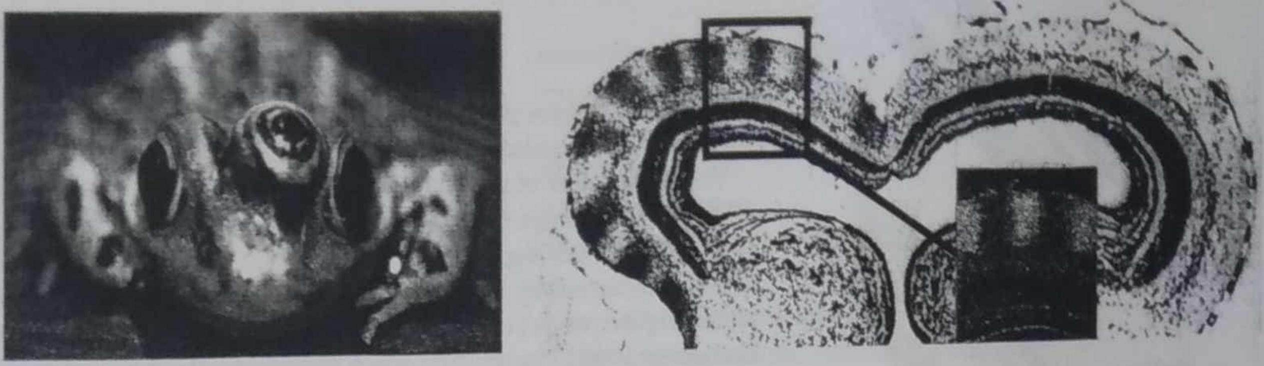
In the 1940s Roger Sperry (1913–1995) began a series of experiments that seemed to emphasize the importance of intrinsic factors, such as genes, for determining the pattern of connections in the brain. If the optic nerve that connects an eye to the brain is cut in an adult mammal, the animal is blinded in that eye and never recovers. In fishes and amphibians such as frogs, however, the animal is only temporarily blinded; in a few months the axons from the eye (specifically, from the ganglion cells of the retina) reinnervate the brain (specifically the dorsal portion of the midbrain, called the *tectum*) and the animal recovers its eyesight. When food is presented on the left or right, above or below, the animal flicks its tongue accurately to retrieve it. Thus, either (1) the retina reestablishes the same pattern of connections to the tectum that was there before surgery and the brain interprets visual information as before, or (2) the retina reinnervates the tectum at random but the rest of the brain learns to interpret the information presented in this new pattern.

Several lines of evidence established that the first hypothesis is correct. One such piece of evidence is that the first-arriving retinal axons sometimes pass over uninnervated tectum to reach their original targets. In the classic case illustrating this phenomenon, the optic nerve was cut and the eye was rotated 180°; when the animal recovered eyesight, it behaved as if the visual image had been rotated 180°, moving to the left when trying to get food presented on the right, and flicking its tongue up when food was presented below. The



7.16 Synaptic Remodeling in the Developing Human Brain Repeated measures from many subjects reveal that the layer of gray matter on the exterior of the cortex becomes thinner across development. Purple and blue depict regions with little change in cortical thickness; yellow and red depict areas that are changing rapidly with age. Note that the prefrontal cortex, usually thought to be important in inhibiting behavior, does not finish maturation until adolescence. (From Gogtay et al., 2004, courtesy of Nitin Gogtay.)

BOX 7.2 (continued)



(B) This three-eyed frog has two eyes innervating the left tectum.

only explanation for this behavior is that the retinal axons had grown back to their *original* positions on the tectum, ignoring the rotation of the eye. Furthermore, once the original connections had been reestablished, the brain interpreted the information as if the eye were in its original position. Even years later, animals that underwent this treatment had not learned to make sense of information from the rotated eye.

Sperry proposed the **chemoaffinity hypothesis** to explain how retinal axons know which part of the tectum to innervate. Suppose each retinal cell and each tectal cell had a specific chemical identity—an address of sorts. Then each retinal cell would need only to seek out the proper address in the tectum and the entire pattern would be reestablished; many chemical cues (represented by many colors in Figure A, *left*) or only a few (two colors in Figure A, *right*) may be involved. Cell adhesion molecules (CAMs) in tectal membranes direct the retinal axons to the roughly appropriate region of tectum (F. Bonhoeffer and Huf, 1985).

But, having arrived at the roughly appropriate region of tectum, retinal connections are fine-tuned by extrinsic factors, specifically by experience. Normally each retina innervates only the tectum on the opposite side. When implantation of a third eye forces two retinas to innervate a single tectum (Figure B, *left*), they each do so in the same rough pattern, but they *segregate*; axons from one retina predominate in one area, and axons from the other retina predominate in neighboring tectum, so there are alternating stripes of innervation from the two eyes (Figure B, *right*).

This segregation depends on activity (Constantine-Paton et al., 1990). If neural activity in one eye is silenced (by injection of drugs), the eye loses its connections to the tectum and the other eye takes over, innervating the entire tectum. If both eyes are silenced (by keeping the animals in the dark), neither eye predominates, their axons fail to segregate in the tectum, and the detailed pattern of innervation fails to appear. Presumably the two eyes are competing for limited supplies of a neurotrophic factor from the tectum, and active synapses take up more of the factor(s).

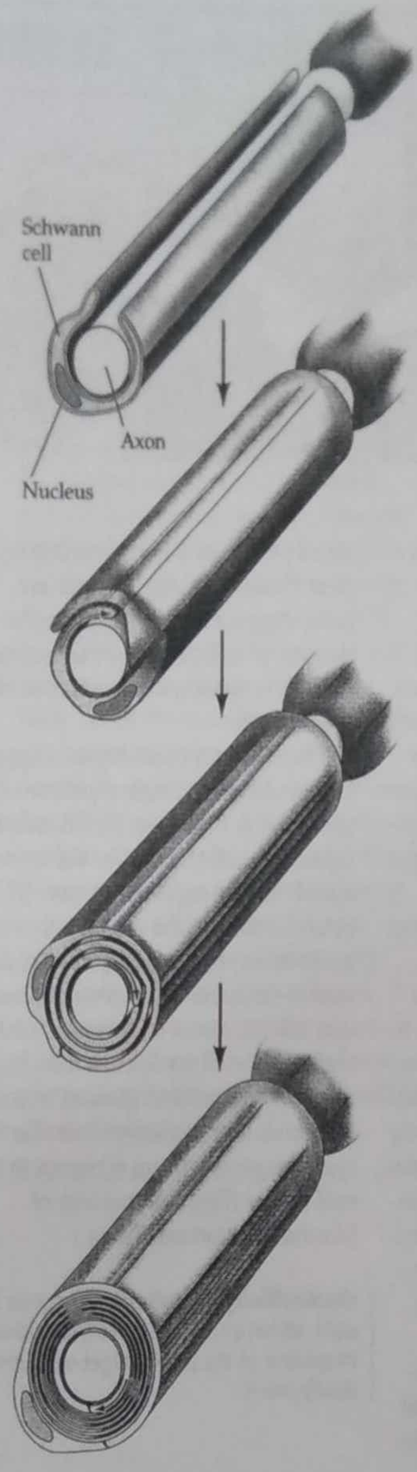
Thus the retinotectal system appears to reestablish the original pattern of innervation in two steps: (1) Chemical cues bring retinal axons to the approximately correct region of tectum. (2) The neural activity of the retinal cells, normally driven by visual experience, directs these axons to innervate or maintain innervation of the precise tectal region. As we'll see later in this chapter, a similar competition goes on in young mammals as information from the two eyes competes to form synapses in visual cortex. (Figure B courtesy of Martha Constantine-Paton.)

chemoaffinity hypothesis The notion that each cell has a chemical identity that directs it to synapse on the proper target cell during development.

Later in this chapter we'll see specific examples in which active synapses are maintained and inactive synapses are retracted in the mammalian visual system. And in Chapter 8 we'll review evidence that synapse rearrangement in the cerebral cortex continues throughout life.

Glial Cells Provide Myelin, Which Is Vital for Brain Function

As already noted, glial cells develop from the same populations of immature cells as neurons. Glial cells continue to be added to the nervous system throughout life. (Sometimes, however, the process becomes aberrant, resulting in glial tumors, or *gliomas*, of the brain.)



7.17 Myelin Formation The repeated wrapping of a Schwann cell cytoplasm around an axon results in a many-layered sheath that insulates the axon electrically, speeding the conduction of electrical signals along its length.

In fact, the most intense phase of glial cell proliferation in many animals occurs *after* birth, when glial cells are added from immature cells located in the ventricular zone.

The development of sheaths around axons—the process of myelination (**Figure 7.17**)—greatly changes the rate at which axons conduct messages (see Figure 3.8). Myelination has a strong impact on behavior because it allows large networks of cells to communicate rapidly. **Multiple sclerosis** is a disorder in which myelin is destroyed, probably by the person's own immune system, in random distinct patches (Manova and Kostadinova, 2000). The resultant desynchronization of activity in these locations can cause devastating disruptions of sensory and motor function.

In humans, the earliest myelination in the peripheral nervous system is evident in cranial and spinal nerves about 24 weeks after conception. But the most intense phase of myelination occurs shortly after birth. Furthermore, some investigators believe that myelin can be added to axons throughout life. The first nerve tracts in the human nervous system to become myelinated are in the spinal cord. Myelination then spreads successively into the hindbrain, midbrain, and forebrain. Within the cerebral cortex, sensory zones are myelinated before motor zones; correspondingly, sensory functions mature before motor functions.

Genes Interact with Experience to Guide Brain Development

Many factors influence the emergence of the form, arrangements, and connections of the developing brain. One influence is genes, which direct the production of every protein that the cell can make. In the nematode *C. elegans*, genes are almost the only factors affecting development; the cells somehow keep track of their mitotic lineage and then simply express the genes that are appropriate for the cell fate that their lineage directs.

Genes are also a major influence on the development of the vertebrate brain. An animal that has inherited an altered gene will make an altered protein, which will affect any cell structure that includes that protein. Thus, every neuronal structure, and therefore every behavior, can be altered by changes in the appropriate gene(s). It is useful to think of genes as *intrinsic* factors—that is, factors that originate within the developing cell itself. All other influences we can consider *extrinsic*—that is, originating outside of the developing cell.

What are the extrinsic factors? One important extrinsic factor is whether the fetus is provided with the nutrients needed to carry out the genetic instructions. As we'll see, the lack of nutrients or the presence of chemicals that interfere with the delivery of nutrients can have a profound effect on brain development.

Another important class of extrinsic factors for all vertebrates is cell–cell interactions: whether a cell expresses a particular gene, takes a particular shape, or performs a particular task may depend on whether neighboring cells exert an inductive influence. The recognition that cell–cell interactions are very important for brain development led to the discovery of another extrinsic factor: neural activity driven by experience.

Genes are the intrinsic factors that influence brain development

Psychologists have shown the importance of genetic factors in a variety of behaviors in many species, including humans (Rende and Plomin, 1995). Of course, genes do not work in isolation. Development should be viewed as the interaction of genetic instructions with the other, extrinsic influences.

The sum of all the intrinsic, genetic information that an individual has is its **genotype**, or **genome**. The sum of all the physical characteristics that make up an individ-

multiple sclerosis Literally "many scars"; a disorder characterized by widespread degeneration of myelin.

genotype or genome All the genetic information that one specific individual has inherited.

TABLE 7.1 Intrinsic and Extrinsic Factors That Affect Neural Development

Factors	Examples of effects
INTRINSIC FACTORS (GENES)	
Chromosomal aberrations	Down syndrome, fragile X syndrome
Single-gene effects	Phenylketonuria, various mutations in *Drosophila*, Tay-Sachs disease
EXTRINSIC FACTORS	
Nutrients	Malnutrition
Drugs, toxins	Fetal alcohol syndrome
Birth process in mammals	Hypoxia-induced mental retardation
Cell–cell interactions	
Induction directs differentiation	Motoneuron differentiation induced by notochord
Neurotrophic factors direct cell death or synapse loss	NGF spares developing sympathetic neurons from death
Thyroid hormone	Deficiency causes severe mental retardation (see Chapter 5)
Neural activity affects synapse maintenance and loss	
Non-sensory-driven	Eye segregation in layer IV cortex before birth
Sensory-driven (experience)	Ocular dominance outside layer IV after birth Increased IQ resulting from childhood enrichment

ual is its **phenotype**. Your genotype was determined at the moment of fertilization and remains the same throughout your life. But your phenotype changes constantly, as you grow up and grow old and even, in a tiny way, as you take each breath.

Phenotype is determined by the interaction of genotype and extrinsic factors, including experience. Thus we'll see that twins who have identical genotypes do not have identical phenotypes, because they have not received identical extrinsic influences. Because their nervous system phenotypes are somewhat different, twins do not behave exactly the same. **Table 7.1** lists intrinsic and extrinsic factors and some of the examples that we'll use to illustrate each.

EFFECTS OF MUTATIONS In rare instances an animal inherits a sudden change in genetic structure, a **mutation**, that is related to marked anatomical or physiological change. Researchers can increase the frequency of mutations by exposing animals to radiation or chemicals that produce changes in genes.

Mutants—animals that display these altered genes—are interesting to study because their changed behavioral phenotype may be quite specific and striking. For example, Greenspan et al. (1980) described mutants of the fruit fly, *Drosophila*, that seemed normal in every way except that they had memory problems. Affectionately labeled *dunce*, *amnesiac*, and *turnip*, these mutants either failed to learn or could learn but forgot rapidly. Biochemical deficits in these mutants (due to mutations that render specific genes, and therefore specific proteins, ineffective) cause the failure of memory (Dudai, 1988).

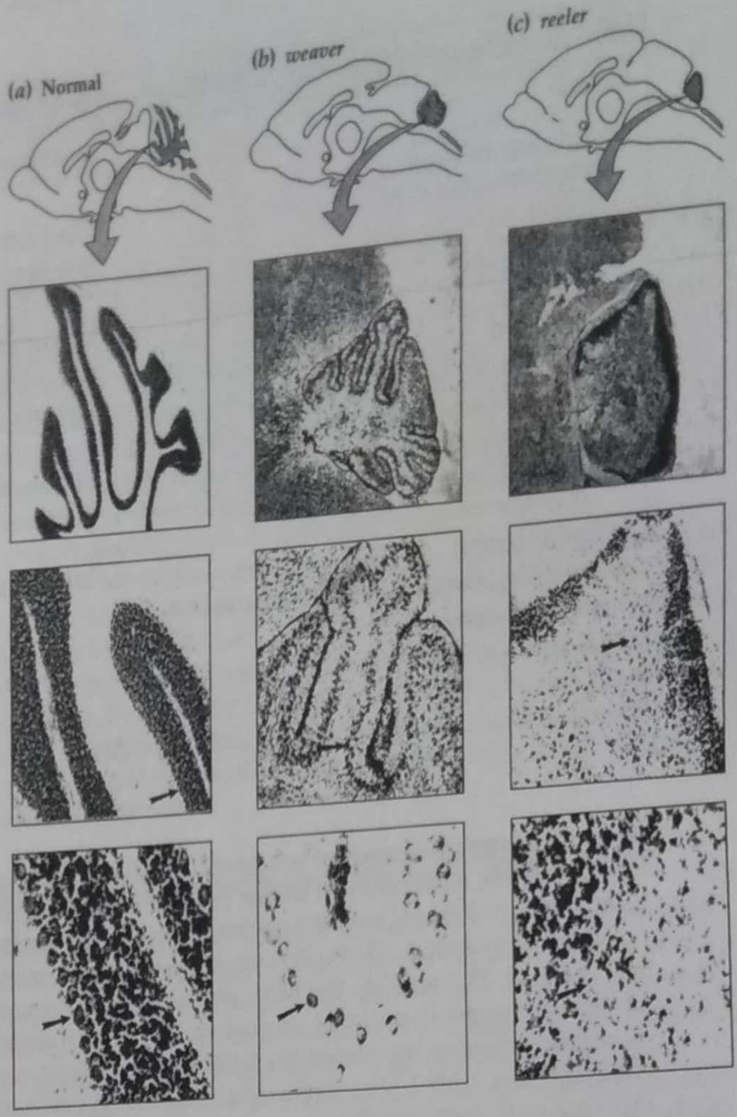
Many mutations in mice affect the nervous system. Members of one group of mouse mutants that is especially intriguing to researchers all have single-gene mutations that affect postnatal development of the cerebellum (Tissir and Goffinet, 2003). The names of these mutant mice—*reeler*, *staggerer*, and *weaver*—reflect the locomotor impairment that characterizes them (**Figure 7.18**). Today scientists deliberately delete or introduce a particular gene in mice in order to study the effect of that gene on the nervous system (**Box 7.3**).

Despite the importance of genes for nervous system development, understanding the genome alone could never enable an understanding of the developing brain because, as we'll see next, experience also directs developing neurons.

phenotype The sum of an individual's physical characteristics at one particular time.

mutation A change in the nucleotide sequence of a gene as a result of unfaithful replication.

mutant An animal carrying a gene that differs from the norm or from the alleles carried by its parents.



7.18 Cerebellar Mutants among Mice (*a*) The cerebellum in a normal mouse at three levels of magnification (25x, 66x, and 250x, from top to bottom). (*b*) In the mutant *weaver*, note the almost complete absence of the tiny granule cells (bottom), while the alignment of the large Purkinje cells (arrows) is normal. (*c*) The mutant *reeler* shows marked derangement of the customary layering of cells. Both mutants show overall shrinkage of the cerebellum (top). (From A. L. Leiman, unpublished observations.)

IDENTICAL GENES, DIFFERENT NERVOUS SYSTEMS One technique produces genetically identical animals, called **clones**, which used to be known mainly in science fiction and horror films. But life imitates fiction. Although the sheep Dolly was the first successfully cloned *mammal*, she was not the first animal to be cloned. In grasshopper clones, the basic shape of larger cells was similar in all clones, but many neurons showed differences in neural connections among these genetically identical individuals (C. Goodman, 1979). Similar results were derived from clones of a tiny crustacean, the daphnia, well known to aquarium owners (Macagno et al., 1973).

Fishes have **identifiable neurons**—called *Mauthner cells*—and in some of these fishes, females produce daughters that are genetically identical to each other and to their mother. Each fish has a single giant Mauthner cell on each side of the brain. Although the pattern of dendritic branching of the Mauthner cells is similar from individual to individual among clones, there are individual differences in the detail of branching and of synapses (Levinthal et al., 1976). Likewise, genetically identical cloned pigs show as much variation in behavior and temperament as do normal siblings (G. S. Archer et al., 2003).

Genetically identical mice raised in different laboratories behave very differently on a variety of tests (Crabbe et al., 1999; Finch and Kirkwood, 2000). One source of variance in mice is the mothering they receive. Genetically identical mice that are raised by different mothers show significant differences in behavior (Francis et al., 2003). For human identical twins, the branching pattern of nerve endings in the skin must differ, since

clones Asexually produced organisms that are genetically identical.

identifiable neurons Neurons that are large and similar from one individual to the next, enabling investigators to recognize them and give them names.

BOX 7.3 Transgenic and Knockout Mice

Animals with mutations in specific genes can offer clues about the role of genes in development and brain function. Until recently, the only types of mutants one could study were the very rare cases of spontaneous mutations or mutations caused by animals being treated with radiation or chemicals to increase the rate of mutation. Unless very small short-lived animals like *Drosophila* were the subject of the research, this process was tedious because very few of the induced mutations were in the gene of interest.

Among the many new tools brought by the revolution in molecular biology is **site-directed mutagenesis**, the ability to cause a mutation in a particular gene. Researchers using this technique must know the sequence of nucleotides in the gene of interest. Then they can use the tendency of complementary nucleotides to hybridize with that part of the gene to induce changes (see the appendix for a refresher on hybridization).

The easiest change to understand is total disruption of the gene, making it nonfunctional. If this is done in special embryonic mouse cells, there are ways to introduce the manipulated cells into the testes or ovaries of a developing mouse. That mouse can then produce offspring that are missing one copy of the gene and, through inbreeding, grandchildren missing both copies of the gene. We call the resulting animal a **knockout organism** because the gene of interest has been *knocked out*.

By following the development of knockout mice, we can obtain clues about the roles of particular genes in normal animals. For example, the motoneurons of brain-derived neurotrophic factor (BDNF) knockout mice survive despite the absence of BDNF (Sendtner et al., 1996), so we know that trophic factor is not crucial for motoneuron survival. On the other hand, some parasympathetic ganglia fail to form in BDNF knockout mice (Erickson et al., 1996), suggesting that these neurons depend on BDNF for survival. As we'll see in Chapter 18, several genes suspected of playing a role in learning have been knocked out in mice, and the resulting animals indeed show deficits in learning.

There are some problems in interpreting such results, because the missing gene may have contributed only very indirectly to the learning process, or the animal's poor performance may have been due to a distraction caused by the knockout. For that matter, even normal behavior by animals missing the gene does not prove that the gene is unimportant for behavior. Perhaps the developing animal, in the absence of that gene, somehow has compensated for the loss and found a new way to solve the problem. This would be another example of the embryonic regulation that is so common in vertebrate development.

In other cases, a functional, manipulated copy of a gene can be introduced into the mouse. This animal is described as **transgenic** because a gene has been *trans*ferred into its genome. Sometimes the introduction of just a single new gene can have a dramatic effect on brain development; for example, compare the brains of newborn mice that are normal with those of transgenic mice carrying a modified gene for β-catenin (see Figure 6.19). Modifying this one gene caused the mouse to make far too many neurons, so extra gyri and sulci developed (Chenn and Walsh, 2002).

The transgenic approach is often used as a method for improving our understanding of genetic disorders. For example, in Chapter 11 we'll learn that when a human gene that causes severe motor impairments is transferred into mice, the mice develop symptoms similar to those that appear in humans. It may be possible to study the disease more closely in these mice and test possible therapies.

Knockout and transgenic animals have one limitation: they possess the genetic manipulation from the moment of conception and in every cell in the body. However, molecular neurobiologists have begun knocking out or replacing a gene in an animal after it has reached adulthood (by injecting the animal with a triggering substance such as tetracycline), or by replacing or knocking out a gene in only one region of the brain. These manipulations allow the animal to develop with a normal genotype, thereby making it easier to interpret the result of the gene manipulation in adulthood. It may even be possible to knock out and then restore a gene in the same individual mouse, tracking its behavior as the gene is lost and regained.

site-directed mutagenesis A technique in molecular biology that changes the sequence of nucleotides in an existing gene.

knockout organism An individual in which a particular gene has been disabled by an experimenter.

transgenic Referring to an animal in which a new or altered gene has been deliberately introduced into the genome.

even identical twins show some differences in their fingerprints (although their prints are more similar than are those of nonidentical twins). Indeed, in several places in this book we find that human identical twins do not always share specific traits—for example, schizophrenia (see Figure 1.8), sexual orientation, or depression. Given that they share the same genes, the behavioral differences between twins are probably due to different experiences.

EXPERIENCE REGULATES GENE EXPRESSION Basic research has revealed one important way in which experience affects the nervous system. Although nearly all of the cells in your body have a complete copy of your genome, each cell uses only a small subset of those genes at any one time. Recall that, when a cell transcribes a particular gene and makes the encoded protein, we say the cell has *expressed* that gene. It turns out that neurons change which genes they are expressing in response to synaptic stimulation. Some genes, called *immediate early genes*, are expressed briefly by almost any neuron that has been stimulated (see Box 2.1).

Neuroscientists exploit this process by exposing an animal to, say, a sound of a particular frequency, and then examining the brain to see which neurons altered gene expression in response to different frequencies. Likewise, lights, odors, or touches will all affect neuronal expression of immediate early genes in particular regions of the brain and spinal cord that receive information about those sensations. Experience also affects the expression of many other genes (Mayfield et al., 2002), not just immediate early genes. So one reason why genetically identical individuals do not have the same brains or behavior is that they are inevitably exposed to different experiences, and they grow up expressing their identical genes in very nonidentical ways (Ridley, 2003).

Experience Is an Important Influence on Brain Development

The young of many species are born in a highly immature state, both anatomically and behaviorally. Varying an individual's experience during early development alters many aspects of behavior, brain anatomy, and brain chemistry in animal models (E. L. Bennett et al., 1964; Gottlieb, 1976; M. R. Rosenzweig and Bennett, 1977, 1978). Presumably, similar neural processes are affected by the early-childhood enrichment programs that produce a long-lasting increase in IQ in humans, especially those from deprived backgrounds (Raine et al., 2002; Ramey et al., 2000).

Visual deprivation can lead to blindness

The role of experience in guiding neural development is best understood in the visual system. Some people do not see forms clearly with one of their eyes, even though the eye is intact and a sharp image is focused on the retina. Such impairments of vision are known as **amblyopia** (from the Greek *amblys*, "dull" or "blunt," and *ops*, "eye"). Some people with this disorder have an eye that is turned inward (cross-eyed) or outward. Children born with such a misalignment see a double image rather than a single fused image. By the time an untreated person reaches the age of 7 or 8, pattern vision in the deviated eye is almost completely suppressed. If the eyes are realigned during childhood, the person learns to fuse the two images and has good depth perception. But if the realignment is not done until adulthood, it's too late to restore acute vision to the turned eye.

Understanding the cause of amblyopia in people has been greatly advanced by visual-deprivation experiments with animals. These experiments revealed startling changes related to disuse of the visual system during early life periods. Depriving animals of light to both eyes (**binocular deprivation**) produces structural changes in visual cortical neurons: a loss of dendritic spines and a reduction in synapses.

If such deprivation is maintained for several weeks during development, when the animal's eyes are opened it will be blind. Although light enters its eyes and the cells of the eyes send messages to the brain, the brain seems to ignore the messages and the animal is unable to detect visual stimuli. If the deprivation lasts long enough, the animal is *never* able to recover eyesight. Thus, early visual experience is crucial for the proper development of vision. There appears to be a **sensitive period** during which these manipulations of experience can exert long-lasting effects on the system. These effects are most extensive during the early period of synaptic development in the visual cortex (**Figure 7.19**). After the sensitive period, the manipulations have little or no effect.

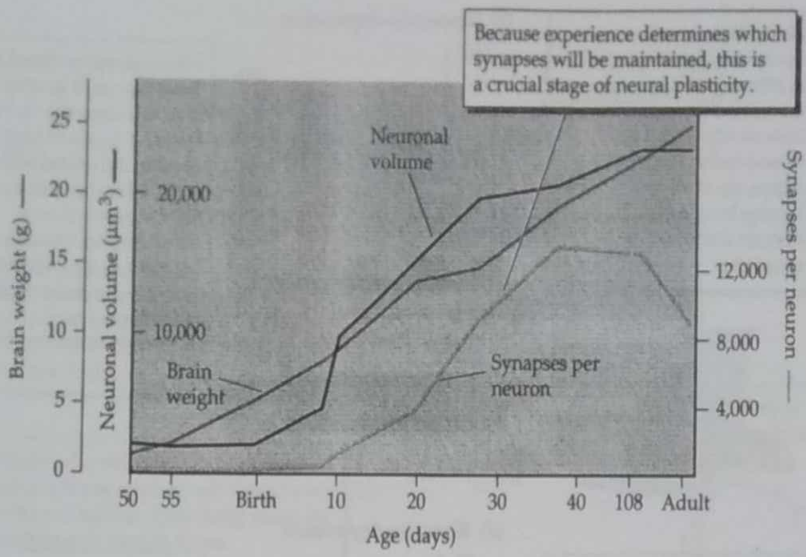
Depriving only one eye of light (**monocular deprivation**) produces profound structural and functional changes in the thalamus and visual cortex. Monocular depriva-

amblyopia Reduced visual acuity that is not caused by optical or retinal impairments.

binocular deprivation Depriving both eyes of form vision, as by sealing the eyelids.

sensitive period The period during development in which an organism can be permanently altered by a particular experience or treatment.

monocular deprivation Depriving one eye of light.


Because experience determines which synapses will be maintained, this is a crucial stage of neural plasticity.

7.19 Brain Development in the Visual Cortex of Cats Synaptic development in cats is most intense from 8 to 37 days after birth, a period during which visual experience can have profound influence. Note that increases in brain weight and cell volume are parallel and precede synaptic development. Note also the decline in synapse numbers after 108 days of age—evidence of synapse rearrangement. (After Cragg, 1975.)

tion in an infant cat or monkey causes the deprived eye not to respond when the animal reaches adulthood. The effect of visual deprivation can be illustrated graphically by an **ocular dominance histogram**, which portrays the strength of response of a brain neuron to stimuli presented to either the left or the right eye. Normally, most cortical neurons (except those in layer IV) are excited equally by light presented to either eye (**Figure 7.20*a***).

Monocular deprivation early in development, by keeping one eye closed or covered, results in a striking shift from the normal graph; most cortical neurons respond only to input from the nondeprived eye (**Figure 7.20*b***). In cats the susceptible period for this effect is the first 4 months of life. In rhesus monkeys the sensitive period extends to age 6 months. After these ages visual deprivation has little effect.

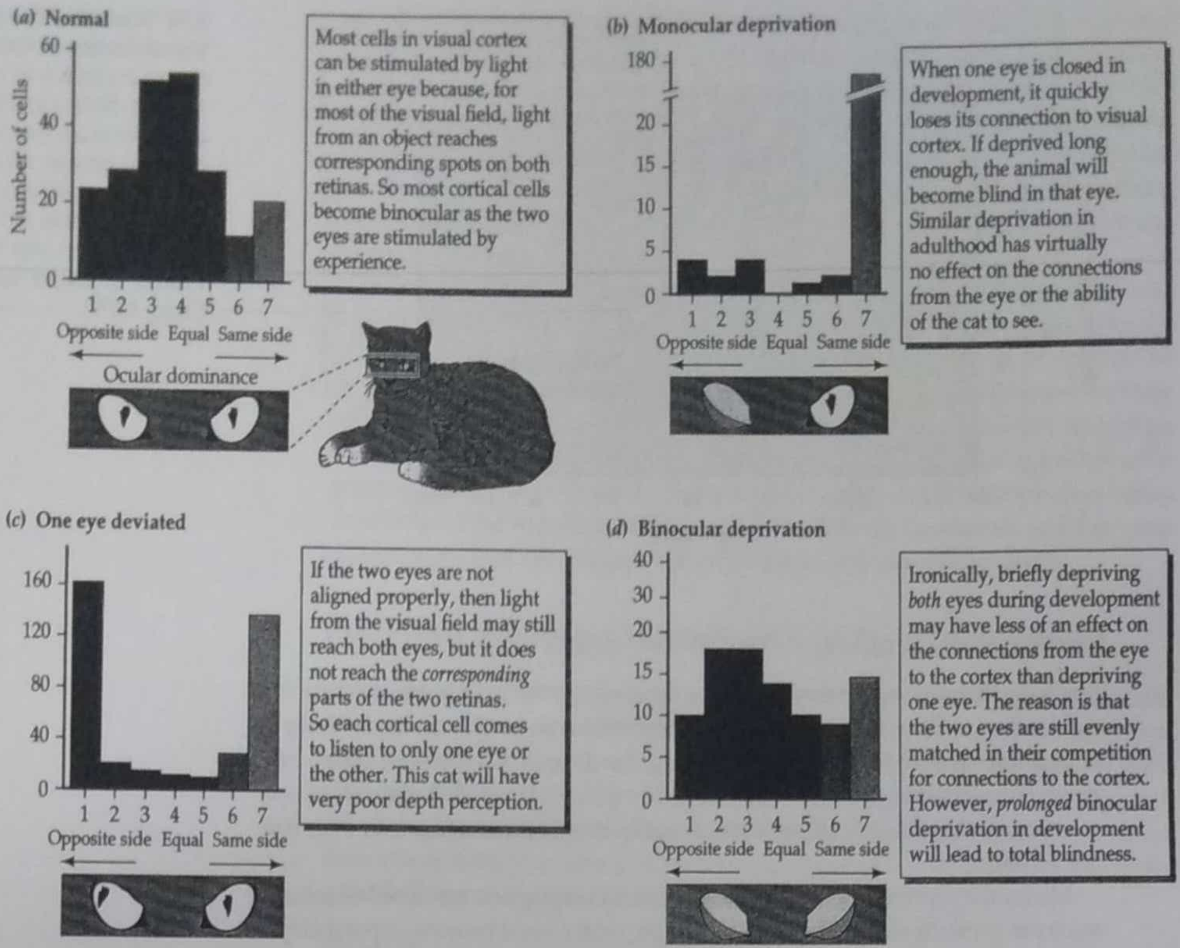
During early development, synapses are rearranged in the visual cortex, and axons representing input from each eye "compete" for synaptic places. Active, effective synapses predominate over inactive synapses. Thus, if one eye is "silenced," synapses carrying information from that eye are retracted while synapses driven by the other eye are maintained. Donald O. Hebb (1949) proposed that effective synapses (those that successfully drive the postsynaptic cell) might grow stronger at the expense of ineffective synapses. Thus, synapses that grow stronger or weaker depending on their effectiveness in driving their target cell are known as **Hebbian synapses** (**Figure 7.21**). In Chapter 18 we will see that the maintenance of active synapses and retraction of inactive synapses may also play a role in learning and memory.

Researchers offer a similar explanation for amblyopia produced by misalignment of the eyes. Hubel and Wiesel (1965) produced an animal replica of this human condition by surgically causing the eyes to diverge in kittens. The ocular dominance histogram of these animals reveals that the normal binocular sensitivity of visual cortical cells is greatly reduced (see Figure 7.20*c*). A much larger proportion of visual cortical cells are excited by stimulation of either the right or the left eye in these animals than in control animals. The reason for this effect is that, after surgery, visual stimuli falling on the misaligned eyes no longer provide simultaneous, convergent input to the cells of the visual cortex.

The competitive interaction between the eyes results in a paradox: brief deprivation of *both* eyes can have less of an effect on neuronal connections than an equal period of deprivation to only one eye has (compare Figure 7.20*a*, *b*, and *d*). Presumably the binocular deprivation keeps both eyes on an equal footing for stimulating cells in the visual cortex, so the predominantly binocular input to the cortical cells is retained.

ocular dominance histogram A graph that portrays the strength of response of a brain neuron to stimuli presented to either the left eye or the right eye.

Hebbian synapse A synapse that is strengthened when it successfully drives the postsynaptic cell.



(a) Normal

Most cells in visual cortex can be stimulated by light in either eye because, for most of the visual field, light from an object reaches corresponding spots on both retinas. So most cortical cells become binocular as the two eyes are stimulated by experience.

(b) Monocular deprivation

When one eye is closed in development, it quickly loses its connection to visual cortex. If deprived long enough, the animal will become blind in that eye. Similar deprivation in adulthood has virtually no effect on the connections from the eye or the ability of the cat to see.

(c) One eye deviated

If the two eyes are not aligned properly, then light from the visual field may still reach both eyes, but it does not reach the *corresponding* parts of the two retinas. So each cortical cell comes to listen to only one eye or the other. This cat will have very poor depth perception.

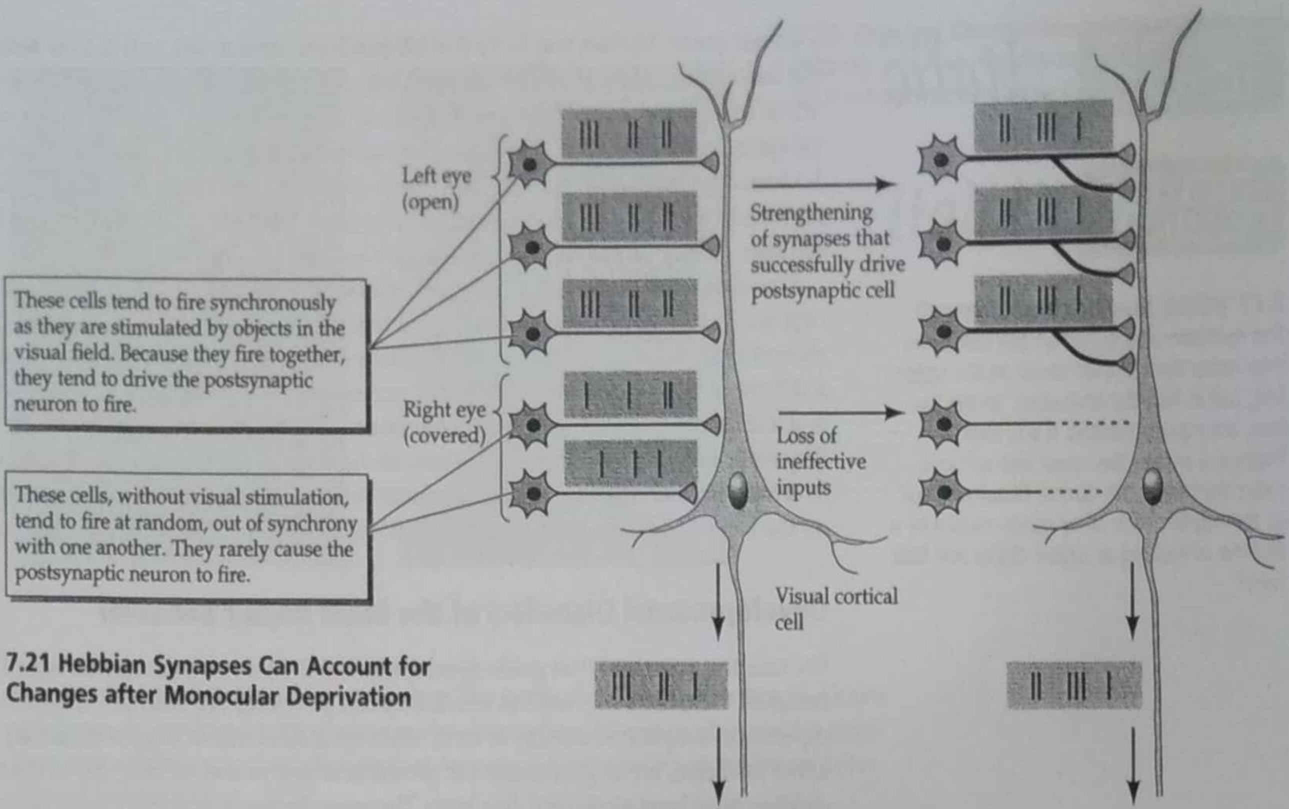
(d) Binocular deprivation

Ironically, briefly depriving *both* eyes during development may have less of an effect on the connections from the eye to the cortex than depriving one eye. The reason is that the two eyes are still evenly matched in their competition for connections to the cortex. However, *prolonged* binocular deprivation in development will lead to total blindness.

7.20 Ocular Dominance Histograms These histograms show responses of cells in the visual cortex of cats in normal adults (*a*); after monocular deprivation through the early critical period (*b*); after early deviation of one eye—that is, squint (*c*); and after binocular deprivation (*d*). The numbers along the *x*-axis represent a gradation in response: Cells that respond *only* to stimulation of the opposite eye are class 1 cells. Cells that respond *mainly* to stimulation of the opposite eye are class 2. Cells that respond equally to either eye are class 4. Cells that respond only to stimulation of the eye on the same side are class 7, and so on. (After Hubel and Wiesel, 1965; Wiesel and Hubel, 1965.)

One popular notion is that neurotrophic factors may be playing a role in experience-driven synapse rearrangement. For example, if the postsynaptic cells are making a limited supply of a neurotrophic factor, and if active synapses take up more of the factor than inactive synapses do, then perhaps the inactive axons retract for lack of neurotrophic factor. If this were the case, then providing all the presynaptic axon terminals with excess neurotrophic factor might delay synapse rearrangement in response to manipulations of visual experience.

Indeed, Cabelli et al. (1995) found that infusions of BDNF (neurotrophin-2) or neurotrophin-4 into the visual cortex of kittens inhibited the loss of synapses. Neither NGF (neurotrophin-1) nor neurotrophin-3 had this effect. Conversely, interfering with the action of BDNF causes the dendrites of neurons in visual cortex to shrink (McAllister et al., 1997), suggesting that this neurotrophic factor normally favors the retention of synapses. Competitive uptake of BDNF has also been implicated in the frog retinotectal system (J. L. Du and Poo, 2004) (see Box 7.2). So perhaps synaptic activity favors presynaptic uptake of neurotrophic factors, and ineffective synapses wither for lack of neurotrophic support.


Left eye
(open)
These cells tend to fire synchronously as they are stimulated by objects in the visual field. Because they fire together, they tend to drive the postsynaptic neuron to fire.
Right eye
(covered)
These cells, without visual stimulation, tend to fire at random, out of synchrony with one another. They rarely cause the postsynaptic neuron to fire.
Strengthening of synapses that successfully drive postsynaptic cell
Loss of ineffective inputs
Visual cortical cell

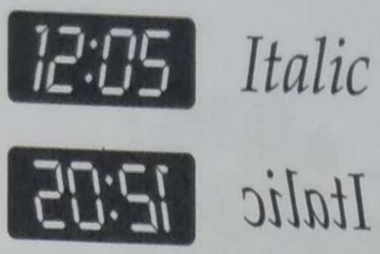
7.21 Hebbian Synapses Can Account for Changes after Monocular Deprivation

Early exposure to visual patterns helps fine-tune connections in the visual system

At birth the visual cortex is quite immature, and most synapses have yet to form. Experiments in which visual inputs are manipulated early in an animal's life have used patterns such as horizontal or vertical lines (Blakemore, 1976), a field of such stripes seen through goggles (H.V. B. Hirsch and Spinelli, 1971), or small spots of light (Pettigrew and Freeman, 1973). In each case, experimenters try to ensure that the animals are exposed to visual stimuli of only one particular type. The results of such experiments suggest that visual experiences during the critical early periods of life can indeed modify the responses of nerve cells in the visual cortex (Movshon and Van Sluyters, 1981). The effects are subtler than those seen with complete deprivation, but the ability of animals to detect visual stimuli of a particular, general pattern (e.g., horizontal lines versus vertical lines) depends on their exposure to such visual patterns during postnatal development.

Human disorders have also proven that early experience is crucial for vision. Babies born with cataracts (cloudy lenses) in industrialized countries usually have them removed a few months after birth and will have good vision. But if such a child grows up with the cataracts in place, removing them in adulthood is ineffective; the person never learns to make use of the information entering the eye (Bower, 2003). Early visual experience is known to be especially crucial for learning to perceive faces, because infants with cataracts that occlude vision for just the first 6 months of life are impaired at recognizing faces even 9 years later (Le Grand et al., 2001). These experience-dependent effects are probably mediated by synapse rearrangement within the visual cortex (Ruthazer et al., 2003).

Why does Michael May, whom we met at the start of the chapter, have such poor vision despite the clear images entering his eye? Had the accident happened to him as an adult, the surgery to let light back into his eye would have restored normal vision. But, like a kitten fitted with opaque contact lenses, Michael was deprived of form vision—in his case, for over 40 years. Because this deprivation began when he was a child, synaptic connections within his visual cortex were not strengthened by the patterns of light moving across the retina. In the absence of patterned stimulation, synapses between the eye and the brain languished and disappeared.



7.22 Which Line Is More Slanted? The numbers and letters on the lower line look more slanted than those on the upper line, but in fact the characters on the two lines are equally slanted. If you look at them in a mirror, the upper line will look more slanted. Is this optical illusion a result of the modification of synapses caused by a lifetime of looking at digital clocks and italic font?

In one sense, Michael was lucky that his blindness came as late as it did. He had normal form vision for the first 3½ years of his life, and that stimulation may have been sufficient to maintain some synapses that would otherwise have been lost. These residual synapses are probably what allow him to make any sense whatsoever of his vision. Michael continues to learn to use sight more and more, even keeping a blog of his experiences (www.senderogroup.com/mike.htm). He loves having sight, but as he himself says, usually he has to "guess" what he's seeing.

One demonstration shows how visual experience in everyday life may affect our perception. In **Figure 7.22**, the numbers and letters along the bottom line appear more slanted than those above, but in fact the slant is the same. One theory of why we see a difference here that doesn't exist is that our experience reading digital clock readouts and italic fonts may tune synapses in our brain to perceive them as more upright than they really are—an effect lost if the figures are backward (Whitaker and McGraw, 2000). In **A Step Further: Experiences in Nonvisual Senses Also Affect Neural Development**, on the website, you can learn how mouse whiskers compete for synapses in the cortex.

Developmental Disorders of the Brain Impair Behavior

Because the processes that guide development of the human brain are so varied and complex, there are many ways in which they can go wrong. For example, children who experience complicated delivery at birth, when a transient lack of oxygen (**hypoxia**) may affect the brain, are at greater risk for mental retardation and schizophrenia than are children who have a problem-free birth. The many factors that control brain development—those that govern cell proliferation, migration, and differentiation, as well as the formation of synapses—are subject to failures that can have catastrophic consequences for adaptive behavior. In other cases, atypical development leads to atypical behavior, but you may find yourself wondering what is or is not a "disorder," as we'll see.

Some genetic disorders have widespread effects on the nervous system

Many genetic disorders affect metabolism and profoundly affect the developing brain. In this category are 100 to 200 different disorders involving disturbances in the metabolism of proteins, carbohydrates, or lipids. Characteristically, the genetic defect is the absence of a particular enzyme that controls a critical biochemical step in the synthesis or breakdown of a vital body product.

An example is **phenylketonuria** (**PKU**), a recessive hereditary disorder of protein metabolism that at one time resulted in many people with mental retardation. One out of 50 persons is a carrier; one in 10,000 births produces an affected victim. The basic defect is the absence of an enzyme necessary to metabolize phenylalanine, an amino acid that is present in many foods. As a result, the brain is damaged by an enormous buildup of phenylalanine.

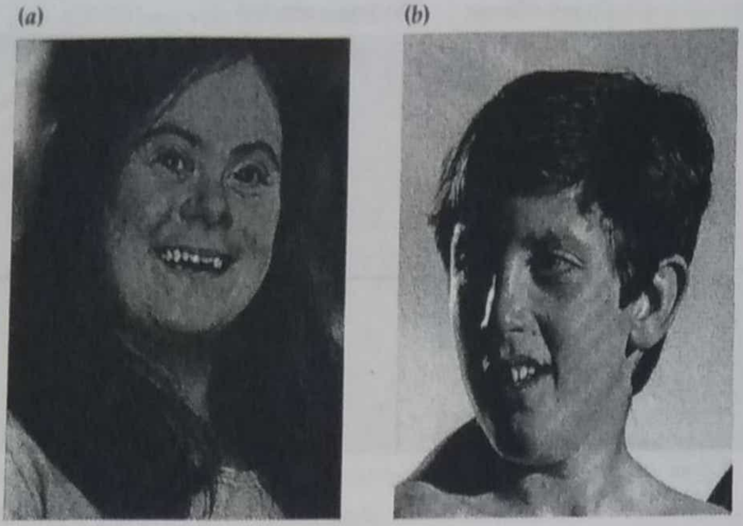
The discovery of PKU marked the first time that an inborn error of metabolism was associated with mental retardation. Screening methods assess the level of phenylalanine in children a few days after birth. Early detection is important because brain impairment can be prevented simply by reducing phenylalanine in the diet. Such dietary control of phenylketonuria is critical during the early years of life, especially before age 2; after that, diet can be relaxed somewhat. Note this important example of the interaction of genes and the environment in PKU: the dysfunctional gene causes mental retardation *only* in the presence of phenylalanine. Reducing phenylalanine consumption reduces or prevents this effect of the gene.

A common form of cognitive disorder resulting from a chromosomal abnormality is **Down syndrome** (**Figure 7.23*a***). People with Down syndrome usually have an extra chromosome 21, for a total of three rather than the typical two copies. This disorder is strikingly related to the age of the mother at the time of conception: for women over 45 years old, the chance of having a baby with Down syndrome is nearly one in 40 (Karp, 1976). The behavioral dysfunctions are quite varied. Most individuals who have Down syndrome have a very low IQ, but some rare individuals attain an IQ as high as 80. Brain

hypoxia A transient lack of oxygen.

phenylketonuria (PKU) An inherited disorder of protein metabolism in which the absence of an enzyme leads to a toxic buildup of certain compounds, causing mental retardation.

Down syndrome Mental retardation that is associated with an extra copy of chromosome 21.



7.23 Atypical Chromosomes Have Widespread Effects (*a*) A young woman with Down syndrome. (*b*) A young man with fragile X syndrome.

abnormalities in Down syndrome also vary. The cerebral cortex of patients with Down syndrome shows abnormal formation of dendritic spines. Mouse models of extra chromosomes result in structural changes that appear analogous to Down syndrome in humans (O'Doherty et al., 2005).

Probably the most frequent cause of inherited mental retardation is the condition **fragile X syndrome** (**Figure 7.23*b***), which is more common in males than in females. At the end of the long arm of the X chromosome is a site that seems fragile—prone to breaking because the DNA there is unstable (Yu et al., 1991). Persons with this abnormality have a modified facial appearance, including elongation of the face, large prominent ears, and a prominent chin. A wide range of cognitive impairments—from mild to severe retardation—are associated with the syndrome (Baumgardner et al., 1994). Cortical neurons from the brains of people with fragile X syndrome, as well as mice genetically engineered to have this syndrome, possess an excess of small, immature dendritic spines (Bagni and Greenough, 2005). These findings suggest that the syndrome affects mental development by blocking the normal elimination of synapses after birth (see Figure 7.11).

The molecular basis of fragile X syndrome provided a surprise for geneticists because it demonstrated that we don't always pass on a faithful copy of our DNA to our offspring. The fragile site in the DNA consists of three nucleotides (CGG; see the appendix for a review of nucleotides) repeated over and over. Most people have only 6 to 50 of these **trinucleotide repeats** at this site (Laxova, 1994). But during the production of sperm or eggs, the number of repeats sometimes changes, so a mother who has only 50 trinucleotide repeats may provide 100 repeats to her son. Any children who receive more than 200 repeats will display fragile X syndrome (Paulson and Fischbeck, 1996). Trinucleotide repeats in a different gene are also at the heart of another behavioral disorder: Huntington's disease (see Chapter 11).

Exposure to drugs during pregnancy can impair neural development

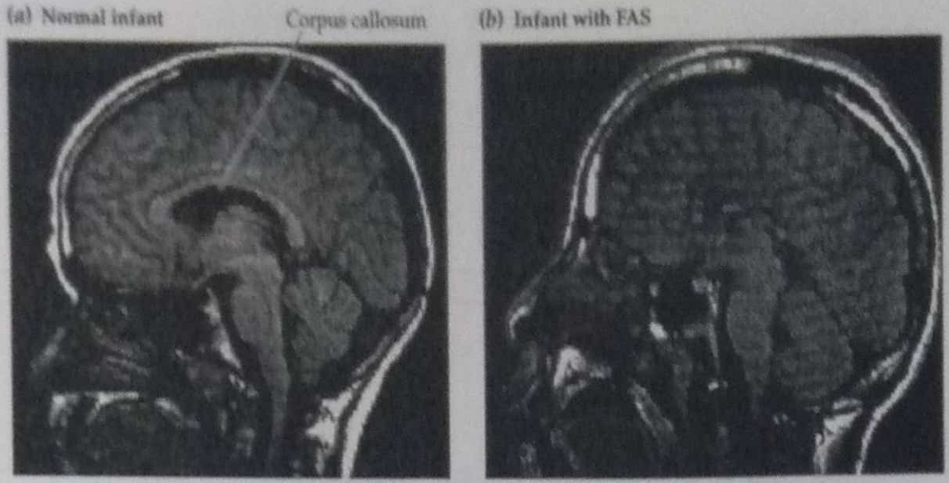
Even in the protected environment of the womb, the embryo and fetus are not immune to outside influence; what is taking place in the mother's body directly affects them. Maternal conditions such as viral infection, exposure to drugs, and malnutrition are especially likely to result in developmental disorders in the unborn child. Concern with the maternal environment as a determinant of brain development spawned the field of **behavioral teratology** (*teratology*—from the Greek *teras*, "monster"—is the study of malformations). Investigators in this field are especially concerned with the pathological effects of drugs ingested during pregnancy.

There is a long history of concern about alcohol and pregnancy, dating back to classical times. Aristotle (quoted in Abel, 1982) warned that "foolish, drunken ... women

fragile X syndrome A condition that is a frequent cause of inherited mental retardation; produced by a fragile site on the X chromosome that seems prone to breaking because the DNA there is unstable.

trinucleotide repeat Repetition of the same three nucleotides within a gene, which can lead to dysfunction, as in the cases of Huntington's disease and fragile X syndrome.

behavioral teratology The study of impairments in behavior that are produced by embryonic or fetal exposure to toxic substances.



7.24 Abnormal Brain Development Associated with Fetal Alcohol Syndrome (a) The brain of a normal infant. (b) The brain of an infant of the same age with FAS. The latter brain shows microcephaly (abnormal smallness), fewer cerebral cortical gyri, and the absence of a corpus callosum connecting the two hemispheres. (Courtesy of E. Riley.)

... bring forth children like unto themselves, morose and languid." By now, the wisdom of this observation (if not the misogyny) is well supported by abundant research. About 40% of children born to alcoholic mothers show a distinctive profile of anatomical, physiological, and behavioral impairments known as **fetal alcohol syndrome (FAS)** (Abel, 1984; Colangelo and Jones, 1982).

Prominent anatomical effects of fetal exposure to alcohol include distinctive changes in facial features (e.g., a sunken nasal bridge and altered shape of the nose and eyelids) and stunted growth. In some cases, the children may lack a corpus callosum (**Figure 7.24**). Few FAS children catch up in the years following birth. The most common problem associated with FAS is mental retardation, which varies in severity. No alcohol threshold has yet been established for this syndrome, but it can occur with relatively moderate intake during pregnancy. Even when FAS is not diagnosed, prenatal exposure to alcohol is correlated with neurophysiological impairments in language and fine motor skills (Mattson et al., 1998).

In addition to mental retardation, children with fetal alcohol syndrome show other neurological abnormalities, such as irritability, tremulousness, and hyperactivity, which we consider next.

Some children have a hard time paying attention in school

The core symptoms of **attention deficit hyperactivity disorder (ADHD)** are distractibility, hyperactivity, and impulsiveness. ADHD is seen in as many as 5% of children and is 2 to 3 times more common in boys than in girls. It is a controversial disorder for several reasons. For one thing, the symptoms are seen in all children at one time or other, so diagnosis depends on the extent to which these commonplace symptoms arise and interfere with normal functioning, rather than on the appearance of any rare or distinctive behavior. When researchers compare children who have been diagnosed with ADHD with other children, the differences they observe suggest that the syndrome is real. For example, children with ADHD have brain volumes that are 3% to 4% smaller than controls, and the difference does not seem to be due to medications taken for the condition (Castellanos et al., 2002). Differences are most prominent in prefrontal cortex (which is thought to play a role in inhibiting behavior; see Chapter 19) and the cerebellum (Arnsten, 2006). Children with ADHD also differ from controls in terms of brain activity (Ashtari et al., 2005), but for all these differences there is considerable overlap between the groups, so none of the differences can be used to diagnose the condition.

Because brain differences and symptoms of ADHD form part of a continuum, one can question whether it is a separate disorder or simply another way in which individuals differ from one another. Even the name may be a misnomer, since many people

fetal alcohol syndrome (FAS) A disorder, including mental retardation and characteristic facial anomalies, that affects children exposed to alcohol (through maternal ingestion) during fetal development.

attention deficit hyperactivity disorder (ADHD) Syndrome of distractibility, impulsiveness, and hyperactivity which, in children, interferes with school performance.

with ADHD have very good attention spans when they're doing something that they find interesting, or something that is more "hands-on." But clearly children with ADHD have difficulty performing well in the traditional classroom.

There is also disagreement about whether ADHD should be treated with drugs, typically stimulants such as methylphenidate (Ritalin) or the amphetamine Adderall. Although the drugs improve attention in children with ADHD (as they do in adults, whether they have ADHD or not), some people question whether the improved performance in school is worth the risk of long-term exposure to psychoactive drugs. The use of ADHD medication is soaring (Kroutil et al., 2006), and these drugs are often abused by people without a medical diagnosis and/or prescription. Reports of serious side effects of stimulant treatment, such as hallucinations (Edelsohn, 2006) and heart attacks (Wilens et al., 2006), complicate the decision of whether to medicate children who have ADHD.

Autism is a disorder of social competence

Autism is a lifelong developmental disorder characterized by impaired social interactions and language, and a narrow range of interests and activities. The disorder is found in about one to two children per thousand, is much more common in males than females, and has a strong heritability (Rapin and Katzman, 1998; Rodier, 2000). Usually autism is discovered when apparently normal toddlers begin regressing, losing language skills, and withdrawing from family interaction. Children with autism may or may not appear mentally deficient, but they tend to **perseverate** (such as by continually nodding the head or making stereotyped finger movements), actively avoid making eye contact with other people, and have a difficult time judging other people's thoughts or feelings. When shown photos of the faces of family members, autistic individuals reveal a pattern of brain activation quite different from that exhibited by controls (Pierce et al., 2001), suggesting a very different brain organization for the fundamental social skill of recognizing others.

Several structural differences between the brains of people with autism and controls have been reported, including a reduction in the size of the corpus callosum and certain cerebellar regions (Egaas et al., 1995). Even though people with autism have fewer neurons in the amygdala than control subjects have (Schumann and Amaral, 2006), they show greater activation of the amygdala when they are gazing at faces (K. M. Dalton et al., 2005). The amygdala has been associated with fear (see Chapter 15), so this finding suggests that children with autism avoid making eye contact with people because they find it aversive.

The underlying problem with autism may be an inability to empathize with others, as reflected in the difficulty that individuals with autism display in making "copycat" movements of the fingers or body. When people with autism do this task, a particular part of the frontal cortex is less activated than in control subjects (Villalobos et al., 2005). The same region is also underactivated when people with autism try to mimic emotional facial expressions of others (**Figure 7.25**) (Dapretto et al., 2006). In monkeys, this hypoactivated region contains *mirror neurons* (discussed further in Chapters 10 and 11), which are active whenever the animal either makes a particular hand movement or sees someone else make that same hand movement. A child with a deficit in such a brain region underlying imitation and empathy might find other people's behaviors so bewildering that he or she would withdraw from social relations and language.

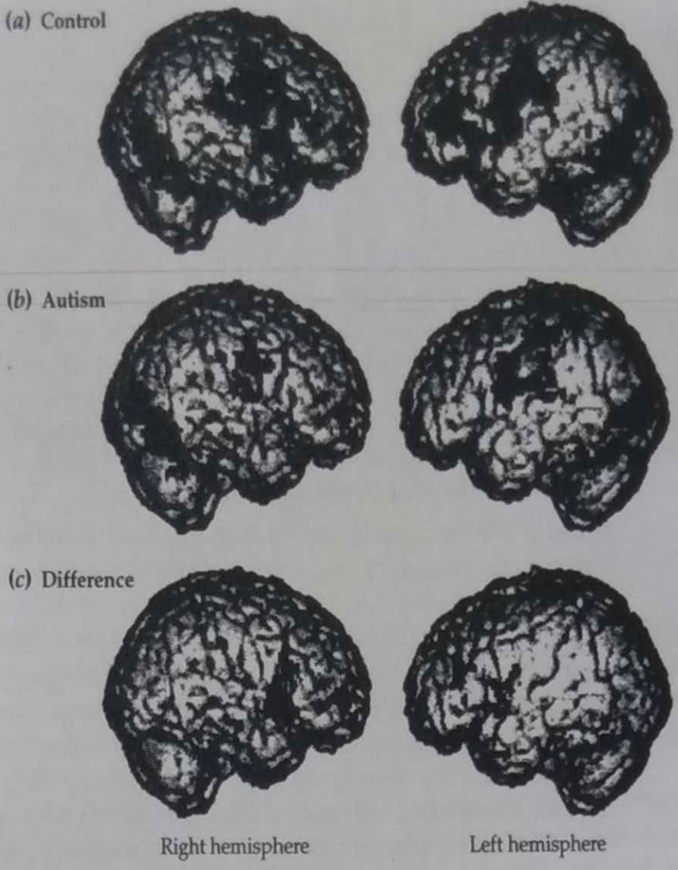
Autism may represent one end of a spectrum. **Asperger's syndrome** is also characterized by difficulties in understanding social interactions, yet children with Asperger's do not lose their language capabilities, and they may indeed be quite articulate. They have difficulty interpreting other people's emotional facial expressions, but they tend to be very good at classifying objects and noting details (Baron-Cohen, 2003). Not surprisingly, individuals with Asperger's tend to become scientists and engineers. The number of children diagnosed with autism and Asperger's is increasing steadily, but no one knows why. One hypothesis is that the mercury in childhood vaccines may act as a neurotoxin that increases the probability of autism disorders, but several studies find no ev-

autism A disorder arising during childhood, characterized by social withdrawal and perseverative behavior.

perseverate To continue to show a behavior repeatedly.

Asperger's syndrome Sometimes called *high-functioning autism*. A syndrome characterized by difficulties in social cognitive processing; usually accompanied by strong language skills.

7.25 Underactivation of Mirror Cells in Autism (a) When control children are asked to imitate the emotional facial expressions displayed in photographs of other people, many brain regions show activation. (b) When children with autism do this task, the same brain regions are active except for a region in the inferior frontal cortex. (c) Mathematical subtraction pinpoints this region to the pars opercularis region that contains "mirror neurons" (see Chapters 10 and 11). This deficit in activating brain regions underlying imitation and empathy may be at the root of the social impairments of autism. (After Dapretto et al., 2006; courtesy of Mirella Dapretto.)



idence of such a link (Madsen et al., 2003). There is no cure for autism, but some children are helped by highly structured training in language and behavior.

The Brain Continues to Change As We Grow Older

The passage of time brings us an accumulation of joys and sorrows—perhaps riches and fame—and a progressive decline in many of our abilities. Although slower responses seem inevitable with aging, many of our cognitive abilities show little change during the adult years, until we reach an advanced age. What happens to brain structure from adolescence to the day when we all become a little forgetful and walk more hesitantly?

Memory impairment correlates with hippocampal shrinkage during aging

In a study of healthy and cognitively normal people, aged 55 to 87, investigators asked whether mild impairment in memory is specifically related to reduction in size of the hippocampal formation (HF) or is better explained by generalized shrinkage of brain tissue (Golomb et al., 1994). (In Chapter 18 we'll see that the hippocampus is implicated in memory.) Volunteers took a series of memory tests and were scored for both immediate recall and delayed recall. A series of ten coronal MRI images for each subject was measured for three variables (**Figure 7.26**): (1) volume of the HF; (2) volume of the supratemporal gyrus, a region that is close to the HF and is known to shrink with age but has not been implicated in memory; and (3) volume of the subarachnoid cerebrospinal fluid (i.e., the fluid-filled space between the interior of the skull and the surface of the brain), which yields a measure of overall shrinkage of the brain. Immediate memory showed very little decline with age, but delayed memory did decline. When effects of sex, age, IQ, and overall brain atrophy were eliminated statistically, HF volume was the only brain measure that correlated significantly with the delayed memory score.

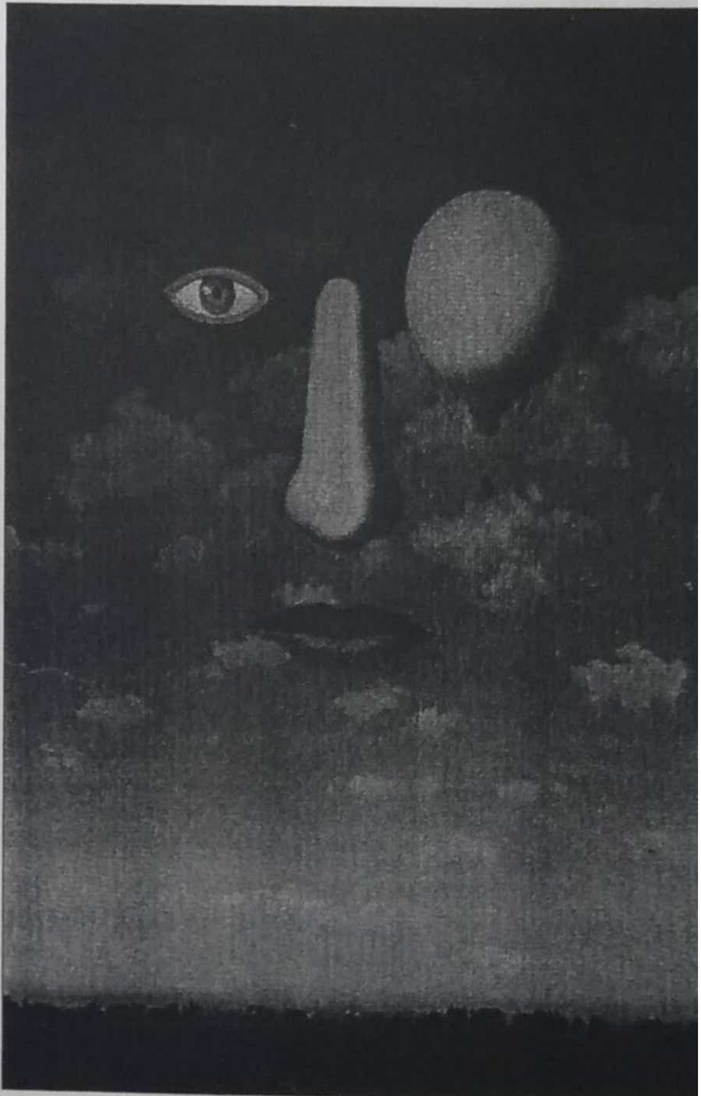
Two regions of the motor system show how different the effects of aging can be. In the motor cortex a type of large neuron—the *Betz cell*—starts to decline in number by about age 50, and by the time a person reaches age 80, many of these cells have shriv-

PART III

PERCEPTION AND ACTION

Light from the sun warms our skin and stimulates our eyes. A chorus of sounds, ranging from the songs of insects to the hearty performances of opera singers, stimulates our ears. Winds bend the hairs on our skin and carry pleasant or unpleasant odors. The food we eat affects receptors in the mouth, the stomach, and the brain. All about us a wide range of energies and substances excites our senses and supplies our brains with a vast array of information about external and internal happenings.

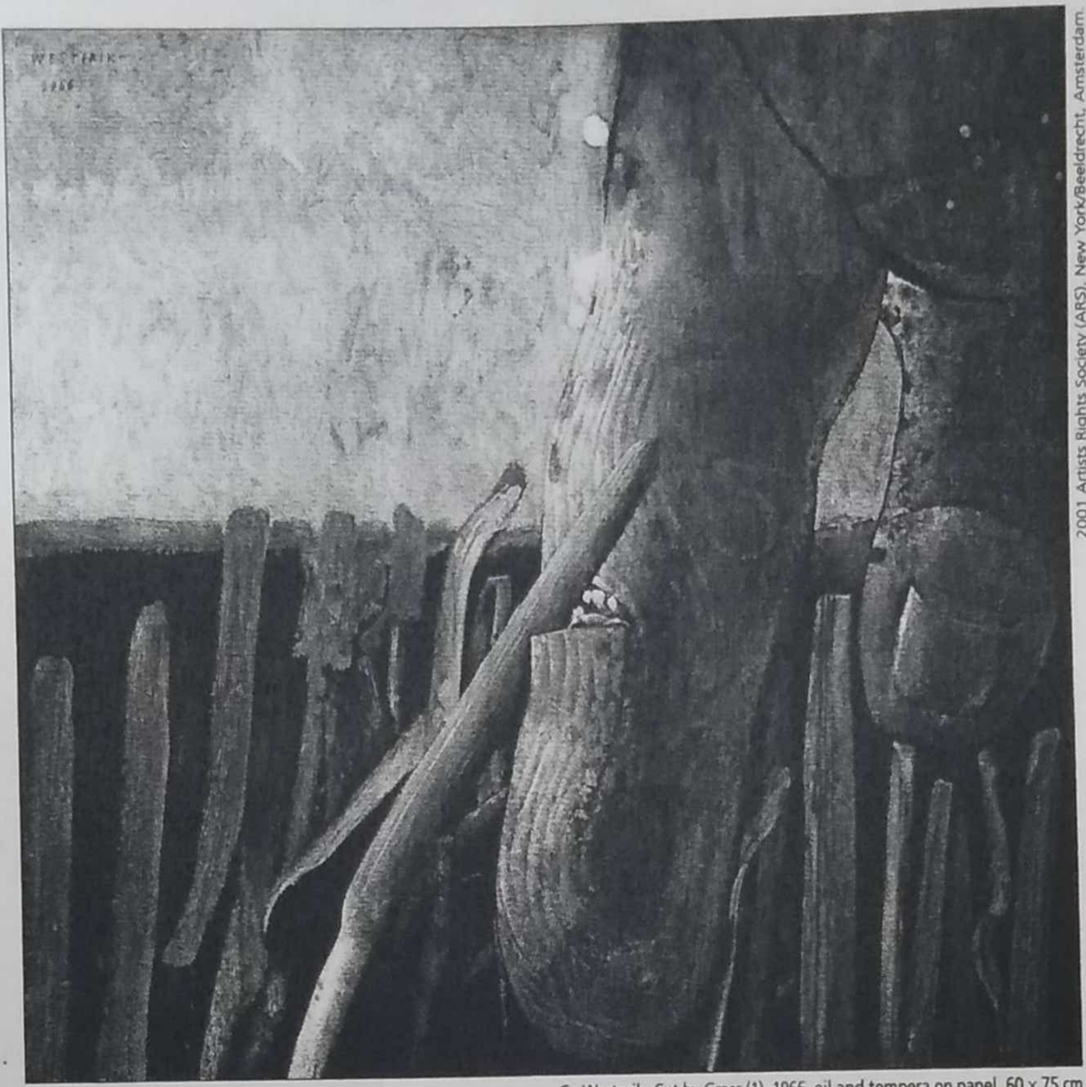
The success of any animal—including humans—in dealing with the tasks of survival depends on its ability to construct reliable representations of the physical characteristics of its environment. In most cases, however, sensory systems are not slavish, passive copiers and reflectors of impinging stimuli—quite the contrary. Evolutionary success calls for far more selective action. For any species, sensory systems construct only partial and selective portraits of the world.



Rene Magritte, *A Beautiful Relationship* (*Les Belles Relations*), 1967, oil on can

Sensory inputs to the brain do not merely provide "pictures in the head"; they often incite the individual to act. Consider the simple case of a sound that occurs suddenly: our eyes almost automatically turn toward the source of the sound. How information is processed in perceptual systems (the topic addressed in Chapters 8 through 10) and then used to choose particular motor responses (Chapter 11) is our theme in Part III.

CHAPTER 8



2001 Artists Rights Society (ARS), New York/Beeldrecht, Amsterdam.

Co Westerik, *Cut by Grass* (1), 1966, oil and tempera on panel, 60 × 75 cm

CONTENTS

Sensory Processing 217

Sensory Receptor Organs Detect Energy or Substances 217

What Type of Stimulus Was That? 219

Sensory Processing Begins in Receptor Cells 221

Sensory Information Processing Is Selective and Analytical 222

Touch: Many Sensations Blended Together 228

Skin Is a Complex Organ That Contains a Variety of Sensory Receptors 228

The Dorsal Column System Carries Somatosensory Information from the Skin to the Brain 230

Pain: An Unpleasant but Adaptive Experience 236

Human Pain Can Be Measured 236

General Principles of Sensory Processing, Touch, and Pain

What's Hot? What's Not?

It was a lovely warm summer evening, perfect for an after-dinner stroll. It was nice to see the neighbors out puttering in their yards, or sitting on the porch sipping cool drinks. When we came upon a woman in matching yellow shorts and blouse sprinkling something on her flowers, I noticed she was using what looked like a big salt shaker. I thought, "Gee, it's not very smart to put insecticide in a salt shaker. What if someone else in the house sprinkles it on food?"

Thinking I would sidle up to the topic to offer her my sage advice, I stopped to ask, "What are you putting on your flowers? Something to kill aphids?" She smiled and said, "No, it's red chili pepper flakes to keep the deer away." She assured me that her treatment worked. When she sprinkled the pepper flakes on the plants in the evening, the flowers would be intact in the morning. If she neglected to treat them in the evening, she would find blossoms missing and telltale bite marks on the bushes come dawn. "Why sprinkle every evening? Do the flakes blow away?" I asked. "Well," she said, "the main problem is that tomorrow the birds come and eat up all the pepper seeds, so I have to put some more on in the evening."

So it turned out that she taught me something: deer hate chili pepper flakes, and birds love them. I was pretty sure I understood why the deer avoid the chili peppers: they contain a chemical called capsaicin that really burns my mouth when I eat spicy food.

But why don't the birds avoid the peppers containing capsaicin? Doesn't it burn their mouths too?

All around us, many different types of energy affect us in various ways. Some molecules traveling through the air cause us to note particular odors. We detect waves of compression and expansion of air as sounds. Our abilities to detect, recognize, and appreciate these varied energies depend on the characteristics of sensory systems. These systems include receptor cells specialized to detect specific energies, as well as spinal cord and brain systems that receive input from these receptors.

For each species, however, certain features of surrounding energies have become especially significant for adaptive success. For example, the bat darting through the evening sky is specially equipped to detect ultrasonic cries. We humans, however, are unable to detect such sounds. Some snakes have infrared-sensing organs that allow them to "see" heat sources in their surroundings, thus enabling them to locate warm-blooded prey. How do animals, including humans, detect changes in the world around them?

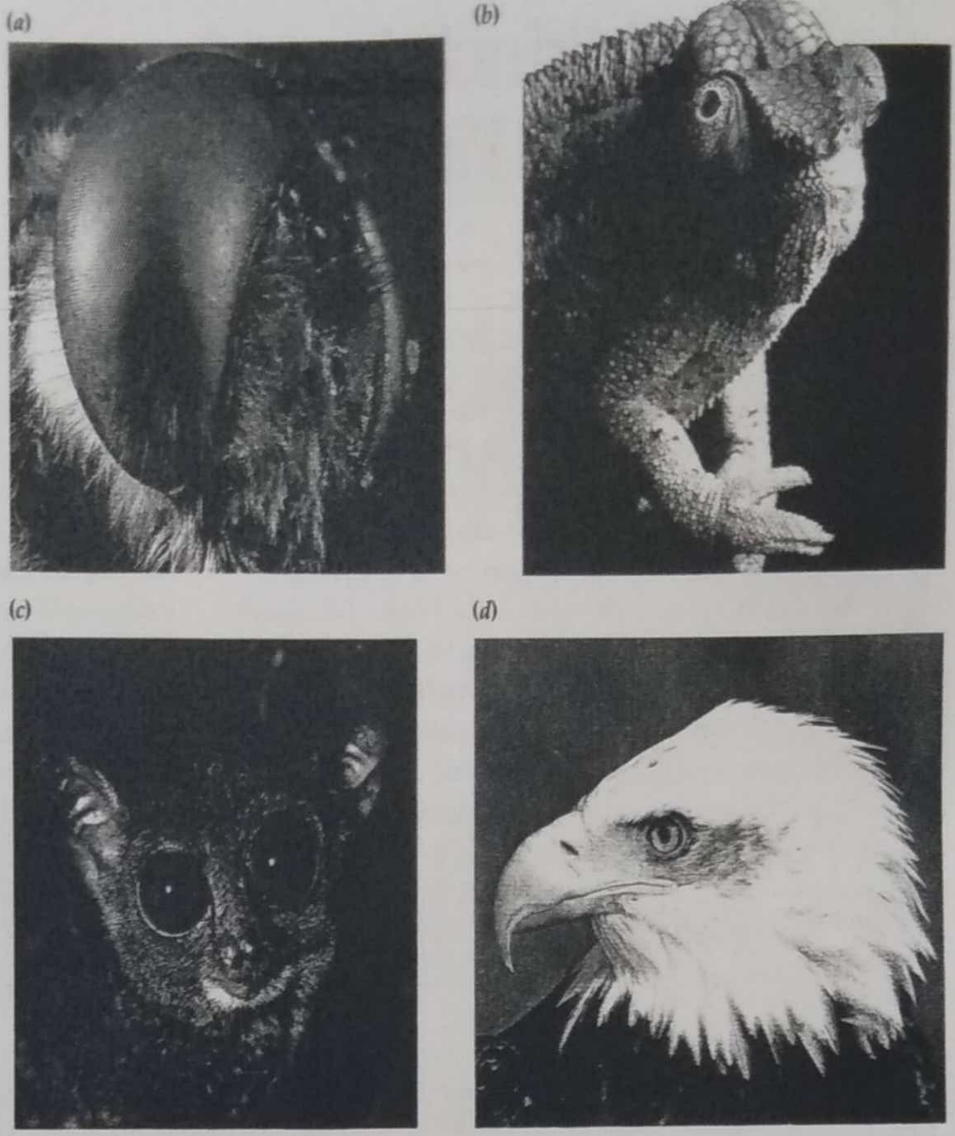
Sensory Processing

Each species has distinctive windows on the world based on which energies it detects and how its nervous system processes that information. In the first portion of this chapter we consider some of the basic principles of sensory processing. Then we look at how those principles apply to touch and pain sensation.

Sensory Receptor Organs Detect Energy or Substances

All animals have specialized body parts that are particularly sensitive to some forms of energy. These **sensory receptor organs** act as filters of the environment: they detect and respond to some events but not others. We call the event that affected the sensory

sensory receptor organ An organ (such as the eye or ear) specialized to receive particular stimuli.



8.1 The Variety of Eyes
(*a*) Honeybees have two kinds of eyes: Between their two large compound eyes, each consisting of thousands of ommatidia, they have three ocelli with a single lens each. (*b*) The panther chameleon can move its two eyes independently. (*c*) The eyes of the Philippine tarsier are specialized for nighttime foraging. (*d*) The eyes of the American bald eagle demonstrate high acuity.

organ a **stimulus** (plural *stimuli*). Stimuli may be sound waves reaching the ear, light entering the eye, or food touching the tongue. **Receptor cells** within the organ detect particular kinds of stimuli and convert them into the language of the nervous system: electrical signals. Eventually information from sensory receptor organs enters the brain as a series of action potentials traveling along millions of axons, and our brains must make sense of it all.

Across the animal kingdom, receptor organs offer enormous diversity. For some snakes, detectors of infrared radiation are essential; several species of fishes detect electrical energy; and some animals detect Earth's magnetic field (Cochran et al., 2004; Holland et al., 2006). The specialized sensors involved in these distinctive forms of detection have evolved to detect signals that are crucial for survival in particular environmental niches. Thus, receptor organs reflect strategies for success in particular worlds.

Even if we consider only a single receptor organ, such as the eye, a wide array of sizes, shapes, and forms reflects the varying survival needs of different animals (**Figure 8.1**). Different kinds of energy, such as light and sound, need different receptor organs to convert them into neural activity, just as taking a photograph requires a camera, not an audiotape recorder.

Table 8.1 classifies sensory systems, identifying the kinds of stimuli detected by sensory receptor organs in each system. An **adequate stimulus** is the type of stimulus for

stimulus A physical event that triggers a sensory response.

receptor cell A specialized cell that responds to a particular energy or substance in the internal or external environment, and converts this energy into a change in the electrical potential across its membrane.

adequate stimulus The type of stimulus for which a given sensory organ is particularly adapted.

TABLE 8.1 Classification of Sensory Systems

Type of sensory system	Modality	Adequate stimuli
Mechanical	Touch	Contact with or deformation of body surface
	Hearing	Sound vibrations in air or water
	Vestibular	Head movement and orientation
	Joint	Position and movement
	Muscle	Tension
Photic	Seeing	Visible radiant energy
Thermal	Cold	Decrease in skin temperature
	Warmth	Increase in skin temperature
Chemical	Smell	Odorous substances dissolved in air or water in the nasal cavity
	Taste	Substances in contact with the tongue or other taste receptor
	Common chemical	Changes in CO_2, pH, osmotic pressure
	Vomeronasal	Pheromones in air or water
Electrical	Electroreception	Differences in density of electrical currents

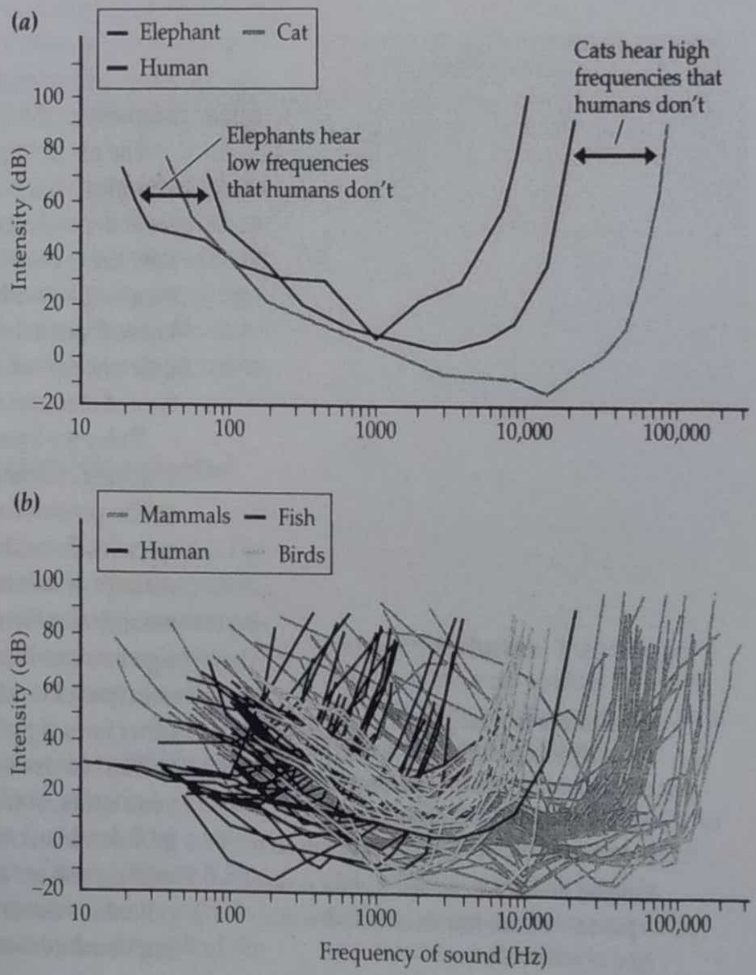
which a given sensory organ is particularly adapted. The adequate stimulus for the eye is photic (light) energy; an electrical shock or pressure on your eye can create an illusory sensation of light (called a *phosphene*), but neither electricity nor mechanical pressure is considered an adequate stimulus for the eye.

Sensory systems of particular animals have a restricted range of responsiveness

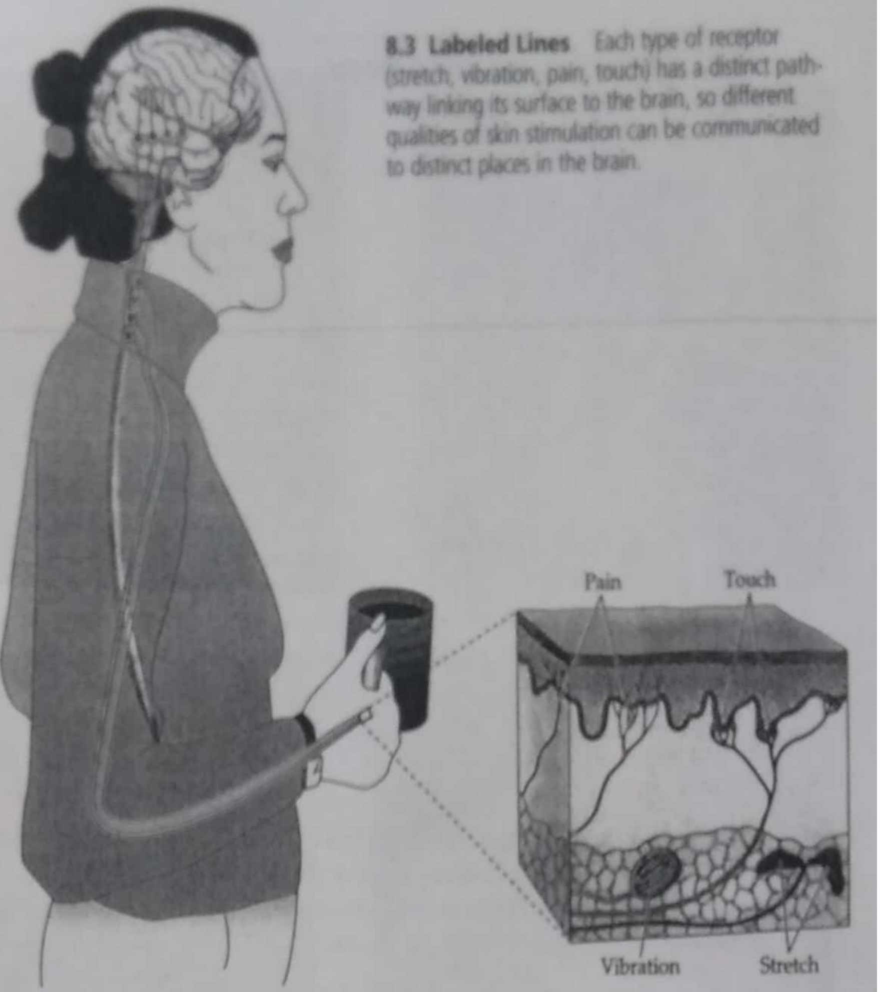
For any single form of physical energy, the sensory systems of a particular animal are quite selective. For example, humans do not hear sounds in the frequency range above 20,000 cycles per second (hertz, Hz)—a range we call *ultrasonic*. To a bat, however, air vibrations of 50,000 Hz would be sound waves, just as vibrations of 5000 Hz are sounds to humans. The range of hearing of larger mammals is even lower than that of humans. **Figure 8.2** compares the auditory ranges of some animals. In the visual realm, too, some animals can detect stimuli that humans cannot. For example, birds and bees see in the ultraviolet range of light.

What Type of Stimulus Was That?

We may appreciate the poet who writes, "The dawn came up like thunder," but usually we want to know whether a sudden dramatic sensory event was auditory or visual,



8.2 Do You Hear What I Hear? For comparison, the auditory sensitivity ranges of three mammals (*a*) and of many species of fishes, birds, and mammals (*b*) are plotted here together. Note that the species within a class detect a similar range of frequencies. For a discussion of the measurement of sound, see Box 9.1. (After Fay, 1988.)



8.3 Labeled Lines Each type of receptor (stretch, vibration, pain, touch) has a distinct pathway linking its surface to the brain, so different qualities of skin stimulation can be communicated to distinct places in the brain.

a touch or a smell. How do we know whether a sudden event was a noise, a flash, or a smack on the head?

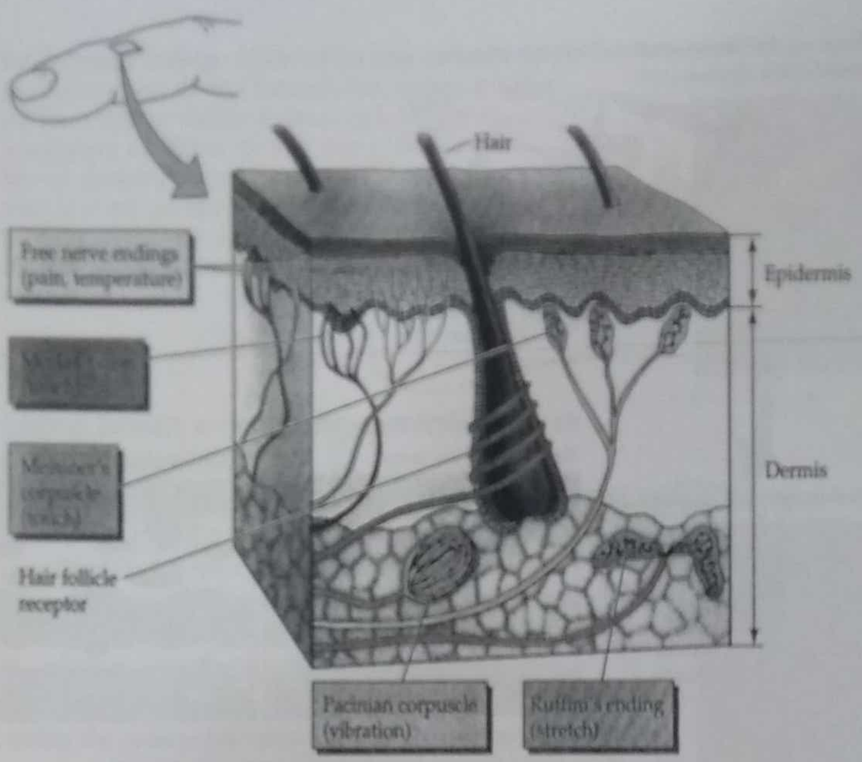
The physiologist Johannes Müller (1801–1858) proposed the doctrine of **specific nerve energies**, which states that the receptors and neural channels for the different senses are independent and that each uses a different nerve "energy." For example, no matter how the eye is stimulated—by light or mechanical pressure or by electrical shock—the resulting sensation is always visual. Müller formulated his hypothesis before anyone knew about action potentials. He imagined that different receptor organs might use a different type of energy to communicate with the brain, and that the brain knew which type of stimulus had happened depending on which type of energy was received.

Today we know that the messages for the different senses—such as seeing, hearing, touching, sensing pain, and sensing temperature—all use the same type of "energy": action potentials. But the brain recognizes the modalities as separate and distinct because each modality sends its action potentials along separate nerve tracts. This is the concept of **labeled lines**: particular nerve cells are, at the outset, labeled for distinctive sensory experiences. Neural activity in one line signals a sound, activity in another line signals a smell, and activity in other lines signals touch. We can even distinguish different types of touch because some lines signal light touch, others signal vibration, and yet other lines signal stretching of the skin (**Figure 8.3**).

You can demonstrate this effect right now. If you take your finger and *gently* press on your eyelid, you'll see a dark blob appear on the edge of your field of view (it helps to look at a blank white wall). Of course your skin also feels the touch of your finger, but why do you *see* a blob with your eye? The energy you applied, pressure, affected action potentials coming from your eye. Because your brain labels that line as always carrying visual information, what you *experienced* was a change in light.

specific nerve energies The doctrine that the receptors and neural channels for the different senses are independent and operate in their own special ways, and can produce only one particular sensation each.

labeled lines The concept that each nerve input to the brain reports only a particular type of information.


Hair
Free nerve endings (pain, temperature)
Meissner's corpuscle (touch)
Hair follicle receptor
Epidermis
Dermis
Pacinian corpuscle (vibration)
Ruffini's ending (stretch)

8.4 Receptors in Skin The main receptors found in human skin are Pacinian corpuscles, Meissner's corpuscles, Merkel's discs, Ruffini's endings, and free nerve endings. The different functions of several of these receptors are compared in Figure 8.12.

Sensory Processing Begins in Receptor Cells

Detection of energy starts with receptor cells. A given receptor cell is specialized to detect particular energies or chemicals. Upon exposure to a stimulus, a receptor cell converts that energy into a change in the electrical potential across its membrane. Changing the signal in this way is called **sensory transduction** (devices that convert energy from one form to another are known as *transducers*, and the process is called *transduction*). Receptor cells are transducers that convert energy around us into neural activity that leads to sensory perception. **Figure 8.4** shows some different receptor cells in skin. We will look at these types in more detail later in the chapter.

Some receptor cells have axons to transmit information. Other receptor cells have no axons of their own but stimulate an associated nerve ending, either mechanically or chemically. For example, various kinds of energy-detecting corpuscles are associated with nerve endings in the skin. The eye has specialized receptor cells that convert light energy into electrical changes that cause neurotransmitter to be released on nearby neurons. The inner ear has specialized hair cells that transduce mechanical energy into electrical signals that stimulate the fibers of the auditory nerve.

The initial stage of sensory processing is a change in electrical potential in receptor cells

The structure of a receptor determines the forms of energy to which it will respond. The steps between the arrival of energy at a receptor cell and the initiation of action potentials in a nerve fiber involve local changes of membrane potential called **generator potentials**. (In most instances, the generator potential resembles the excitatory postsynaptic potentials discussed in Chapter 3.) These electrical changes are the necessary and sufficient conditions for generating action potentials.

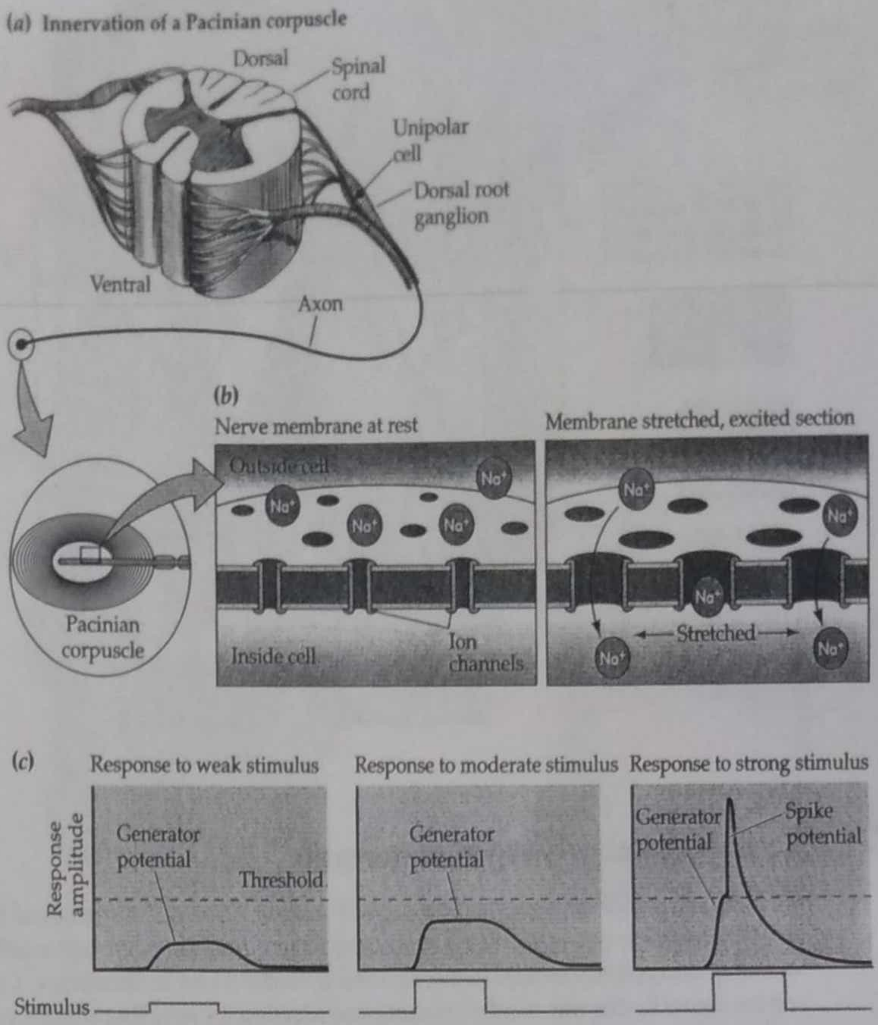
One example of the generator potential can be studied in a receptor called the **Pacinian corpuscle** (Loewenstein, 1971). This receptor, which detects vibration, is found throughout the body in skin and muscle. It is made of an axon surrounded by a structure that resembles a tiny onion because it has concentric layers of tissue (**Figure 8.5*a***).

Mechanical stimuli (in this case vibration) delivered to the corpuscle produce a graded electrical potential with an amplitude that is directly proportional to the strength of the

sensory transduction The process in which a receptor cell converts the energy in a stimulus into a change in the electrical potential across its membrane.

generator potential A local change in the resting potential of a receptor cell that mediates between the impact of stimuli and the initiation of nerve impulses.

Pacinian corpuscle A skin receptor cell type that detects vibration.


(a) Innervation of a Pacinian corpuscle
Dorsal
Spinal cord
Unipolar cell
Dorsal root ganglion
Ventral
Axon
Pacinian corpuscle
(b)
Nerve membrane at rest
Outside cell
Na+
Inside cell
Ion channels
Membrane stretched, excited section
Stretched
(c)
Response to weak stimulus
Response to moderate stimulus
Response to strong stimulus
Response amplitude
Generator potential
Threshold
Spike potential
Stimulus

8.5 The Structure and Function of the Pacinian Corpuscle (*a*) The Pacinian corpuscle surrounds an afferent nerve fiber ending. (*b*) When the nerve membrane is at rest (*left*), the ion channels are too narrow to admit sodium ions (Na^+). Vibration applied to the corpuscle (*right*) stretches part of the neuronal membrane, enlarging the ion channels and permitting the entry of Na^+, which initiates an action potential. (*c*) The neuron shows increasing response to stimuli of increasing intensity until it reaches threshold, triggering an action potential.

stimulus. When this generator potential gets big enough, an action potential is generated and we say that the receptor has reached **threshold**. Careful dissection of the corpuscle, leaving the bared axon intact, shows that this graded potential—the generator potential—is initiated in the axon terminal itself. The sequence of excitatory events is as follows:

1. Mechanical stimulation deforms the corpuscle.
2. This deformation leads to mechanical stretch of the tip of the axon.
3. Stretching the axon opens mechanically gated ion channels in the membrane, allowing sodium ions to enter (**Figure 8.5*b***).
4. When the generator potential reaches threshold amplitude, the axon produces one or more action potentials (**Figure 8.5*c***).

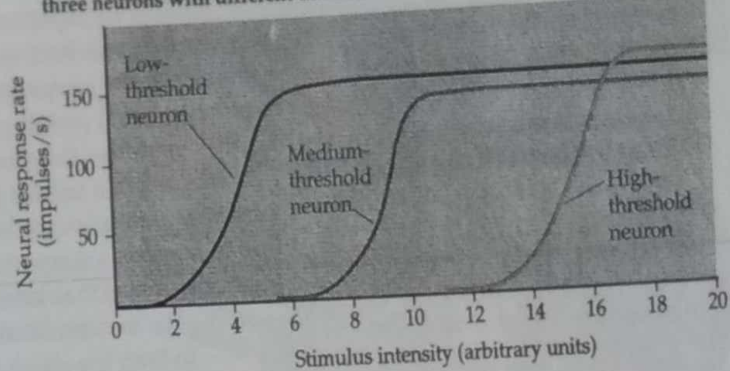
Sensory Information Processing Is Selective and Analytical

Thinkers in ancient Greece believed that nerves were tubes through which tiny bits of stimulus objects traveled to the brain, to be analyzed and recognized there. (Imagine the nerves in your tongue sending minuscule chunks of garlic to your brain for analysis.) Even after learning about neural conduction in the twentieth century, many investigators thought that the sensory nerves simply transmitted accurate information about stimulation to the brain centers. Now, however, it is clear that the sensory organs and peripheral sensory pathways convey only limited—*even distorted*—information to the brain. A good deal of selection and analysis takes place in the peripheral sensory pathways. In the discussion that follows we will examine six aspects of sensory processing: coding, adaptation, pathways, suppression, receptive fields, and attention.

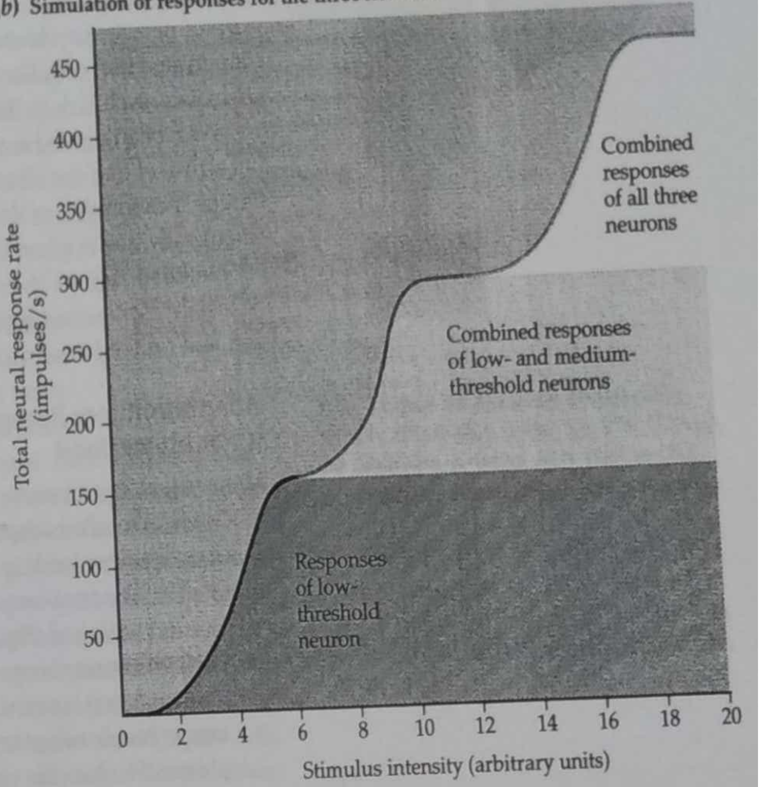
threshold The stimulus intensity that is just adequate to trigger a nerve impulse in the axon.

8.6 Intensity Coding (a) Each of the three nerve cells represented here has a different threshold—low, medium, or high—and thus a different response to stimuli. Each cell varies its response over a *fraction* of the total range of stimulus intensities—an example of range fractionation. (b) Although none of these nerve cells can respond faster than 150 times per second, the sum of all three can vary in response rate from 0 to 450 impulses per second, accurately indicating the intensity of the stimulus.

(*a*) **Response rate versus stimulus intensity for three neurons with different thresholds**



(*b*) **Simulation of responses for the three neurons**



Coding: Sensory events are represented by action potentials

Information about the world is represented in the nervous system by electrical potentials in cells. We have already considered the first steps in this process—the transduction of energy at receptors, the generator potential, and the creation of action potentials in sensory neurons. But how does this neural activity "stand for" (or *represent*) the stimuli impinging on the organism? Through some form of **coding**, the pattern of electrical activity in the sensory system must convey information about the original stimulus. Neural codes are limited in that each action potential is always the same size and duration, so sensory information is encoded by other features of neural activity, such as the number and frequency of the action potentials, the rhythm in which clusters of action potentials occur, and so on. Let's examine neural representations of the intensity and location of stimuli.

STIMULUS INTENSITY We respond to sensory stimuli over a wide range of intensities. Furthermore, within this range we can detect small differences of intensity. How are different intensities of a stimulus represented in the nervous system? A single nerve cell could represent the intensity of the stimulus by changing the frequency of action potentials transmitted (**Figure 8.6*a***). However, only a limited range of different sensory intensities can be represented in this manner because neurons can fire only so fast.

As we noted in Chapter 3, the maximal rate of firing for a single nerve cell is about 1200 action potentials per second, and most sensory fibers do not fire more than a few hundred action potentials per second. But the number of differences in intensity that can be detected in vision and hearing is much, much greater than this code can offer. For example, we can see both in very dim light and when the light is 10 billion–fold brighter. A *single* receptor that could change activity only a few hundred–fold could never represent that entire range.

Multiple receptor cells acting in a parallel manner provide a broader range for coding the intensity of a stimulus. As the strength of a stimulus increases, new nerve cells are "recruited"; thus, intensity can be represented by the number of active cells. **Range fractionation** takes place when different receptor cells are "specialists" in particular segments, or *fractions*, of an intensity scale (**Figure 8.6*b***). This mode of stimulus coding requires an array of receptors and nerve cells that differ in threshold to fire. Some sensory neurons have a very low threshold (so they are highly sensitive); others have a much higher threshold (so they are less sensitive). Thus, one clue to the intensity of a stimulus is whether it activated only low-threshold receptors, or both low- and high-threshold receptors.

coding The rules by which action potential in a sensory system reflect a physical stimulus.

range fractionation A hypothesis of stimulus intensity perception stating that a wide range of intensity values can be encoded by a group of cells, each of which is a specialist for a particular range of stimulus intensities.

somatosensory Body sensation, referring to touch and pain sensation.

adaptation The progressive loss of receptor sensitivity as stimulation is maintained.

tonic receptor A receptor in which the frequency of nerve impulse discharge declines slowly or not at all as stimulation is maintained.

phasic receptor A receptor in which the frequency of nerve impulse discharge drops rapidly as stimulation is maintained.

STIMULUS LOCATION The position of an object or event, either outside or inside th body, is an important piece of information. Did something just poke my foot or m hand? Some sensory systems reveal this information by the position of excited recep tors on the sensory surface. This feature is most evident in the **somatosensory** ("bod sensation") system.

You know that an object is on your back if a receptor in the skin there is stimulate If a receptor on your palm is stimulated, then the object must be there. Each recepto activates pathways that convey unique positional information. The spatial properties a stimulus are represented by labeled lines that uniquely convey spatial information Similarly, in the visual system an object's spatial location determines which receptors i the eye are stimulated.

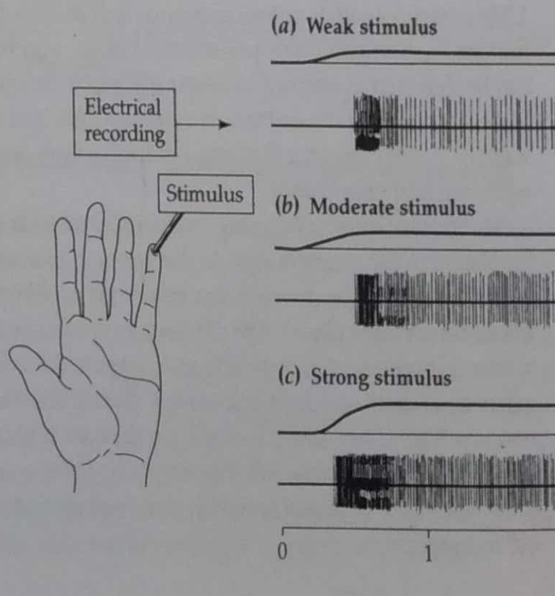
In both the visual and the touch system, cells at all levels of the nervous system from the surface sheet of receptors to the cerebral cortex—are arranged in an orderl maplike manner. The map at each level is not exact, but reflects both position and re ceptor density. More cells are allocated to the spatial representation of sensitive, densel innervated sites like the skin of the lips or the center of the eye, than to sites that are les sensitive, such as the skin of the back or the periphery of the eye.

With bilateral receptor systems—the two ears or the two nostrils—the relative tim of arrival of the stimulus at the two receptors, or the relative intensity, is directly relate to the location of the stimulus. For example, the only time when both ears are excite identically is when the sound source is equidistant from the ears, in the median plan of the head. As the stimulus moves to the left or right, receptors of the left and righ sides are excited asymmetrically. Specialized nerve cells that receive inputs from bot left and right ears to determine where sounds come from are discussed in Chapter 9.

Adaptation: Receptor response can decline even if the stimulus is maintained

Many receptors show progressive loss of response when stimulation is maintained. Th process is called **adaptation**. We can demonstrate adaptation by recording action pote tials in a fiber leading from a sensory receptor that is receiving a constant level of sti ulation. The frequency of action potentials progressively declines, even though the sti ulus is continued (**Figure 8.7**). In terms of adaptation, there are two kinds of recepto **Tonic receptors** show a slow or nonexistent decline in the frequency of action potenti as stimulation is maintained; in other words, these receptors show relatively little ada tation. **Phasic receptors** display adaptation, rapidly decreasing the frequency of acti potentials when the stimulus is maintained.

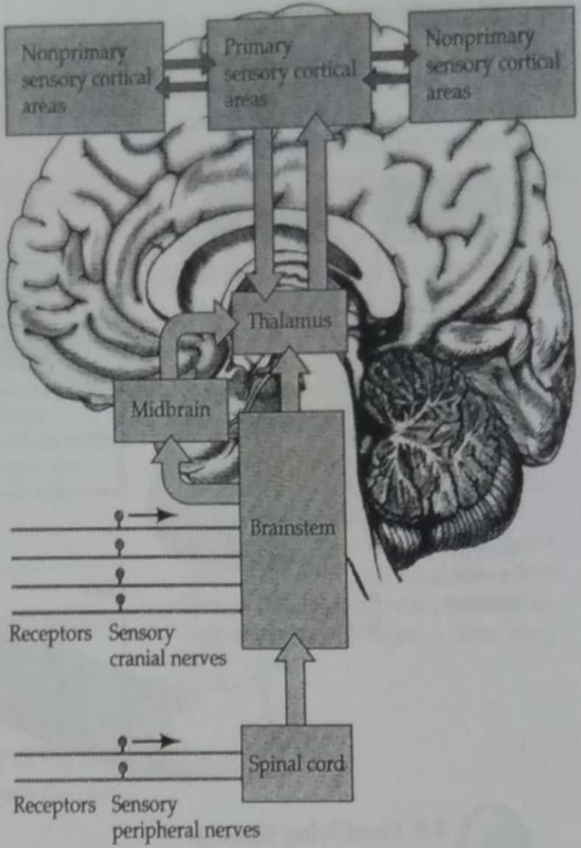
Adaptation means that there is a progressive shift in neural activity *away from ac rate portrayal* of maintained physical events. Thus the nervous system may fail to regis



8.7 Sensory Adaptation The neuron represented here, whose receptive field is located on the fifth finger, fires rapidly when the stimulus—whether weak (*a*), moderate (*b*), or strong (*c*)—is first applied, but then it adapts, slowing to a steady rate. (After Knibestol and Valbo, 1970.)

neural activity even though the stimulus continues. Such a striking discrepancy is no accident; sensory systems emphasize *change* in stimuli because changes are more likely to be significant for survival. Sensory adaptation prevents the nervous system from becoming overwhelmed by stimuli that offer very little "news" about the world. For example, your pants may press a hair on your leg continuously, but you're saved from a constant neural barrage from this stimulus by several mechanisms, including adaptation.

The basis of adaptation includes both neural and nonneural events. For example, in some mechanical receptors, adaptation develops from the elasticity of the receptor cell itself. This situation is especially evident in the Pacinian corpuscle, which detects vibration (see Figure 8.5). Maintained vibration on the receptor results in an initial burst of neural activity and a rapid decrease to almost nothing. But when the corpuscle (which is a separate, accessory cell) is removed, the same constant stimulus applied to the uncovered sensory nerve fiber produces a continuing discharge of action potentials. So for this receptor, adaptation is a mechanical property of the nonneural component, the corpuscle rather than the axon.


Nonprimary sensory cortical areas
Primary sensory cortical areas
Nonprimary sensory cortical areas
Thalamus
Midbrain
Brainstem
Receptors
Sensory cranial nerves
Spinal cord
Receptors
Sensory peripheral nerves

8.8 Levels of Sensory Processing Sensory information enters the CNS through the brainstem or spinal cord, then reaches the thalamus. The thalamus shares the information with the cerebral cortex; the cortex directs the thalamus to suppress some sensations. Primary sensory cortex swaps information with nonprimary sensory cortex. This organization is present in all sensory systems except smell (see Chapter 9).

Pathways: Successive levels of the CNS process sensory information

Sensory information travels from the sensory surface to the highest levels of the brain, and each sensory system has its own distinctive pathway. Pathways from receptors lead into the spinal cord or brainstem, where they connect to distinct clusters of nerve cells. These cells, in turn, have axons that connect to other nerve cell groups. Each sensory modality—such as touch, vision, or hearing—has a distinct hierarchy of tracts and stations in the brain that are collectively known as the **sensory pathway** for that modality.

Each station in the pathway accomplishes a basic aspect of information processing. For example, painful stimulation of the finger leads to reflex withdrawal of the hand, which is mediated by spinal circuits. At the brainstem level, other circuits can turn the head toward the source of pain. Eventually sensory pathways terminate in the cerebral cortex, where the most complex aspects of sensory processing take place. For most senses, information reaches the **thalamus** before being relayed to the cortex (**Figure 8.8**). Information about each sensory modality is sent to a separate division of the thalamus.

Suppression: Sometimes we need receptors to be quiet

We have noted that successful survival does not depend on exact reporting of stimuli. Rather, our success as a species demands that our sensory systems accentuate, from among the many things happening about us, the important *changes* of stimuli. We just discussed how sensory receptor adaptation can suppress a constant stimulus, but two other suppression strategies are also available.

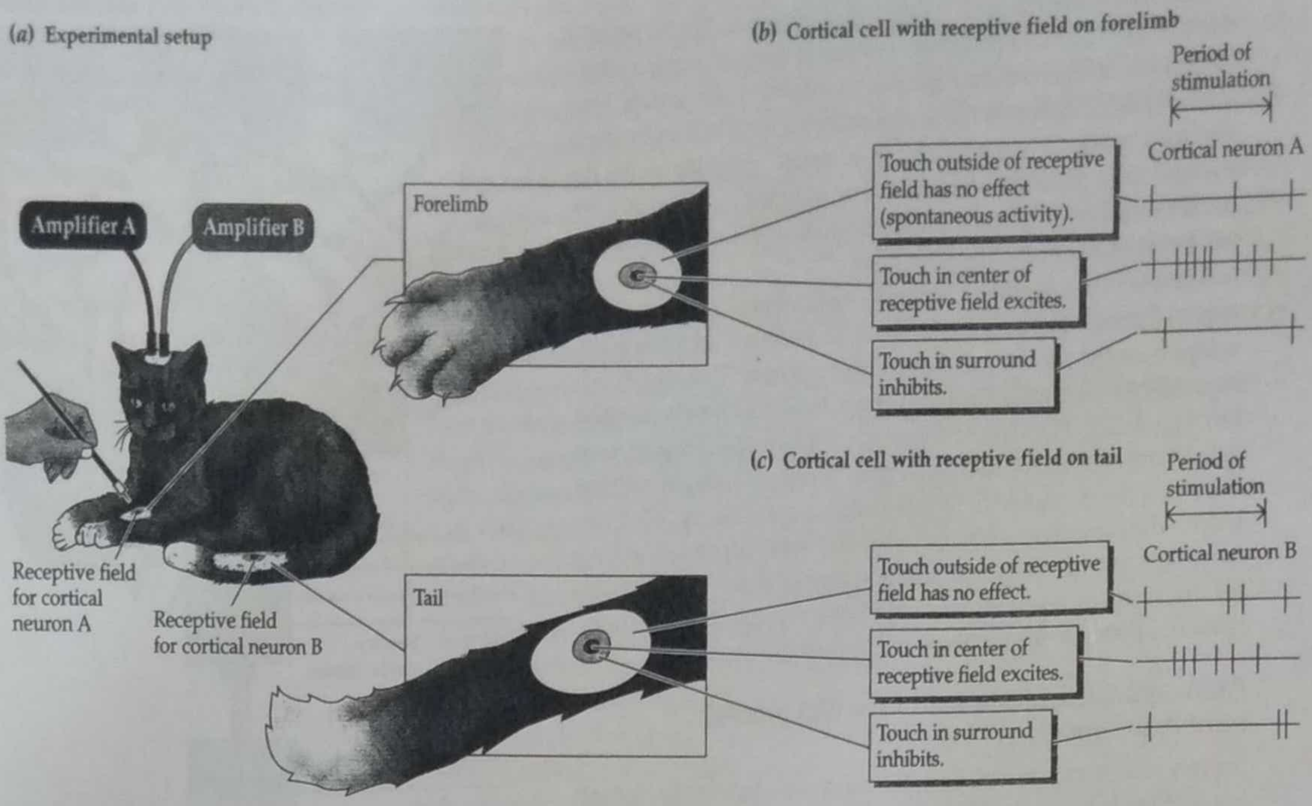
In many sensory systems, accessory structures can reduce the level of input in the sensory pathway. For example, closing the eyelids reduces the amount of light that reaches the retina. In the auditory system, contraction of the middle-ear muscles reduces the intensity of sounds that reach the inner ear. In this form of sensory control, the relevant mechanisms change the intensity of the stimulus before it reaches the receptors.

In a second form of information control, neural connections descend from the brain to lower stations in the sensory pathway, in some cases as far as the receptor surface. For example, higher centers in the pain system (discussed later in this chapter) send axons down the spinal cord, where they can inhibit incoming pain signals. This **central modulation of sensory information** is also evident in the auditory system, where a small group of cells in the brainstem sends axons along the auditory nerve to connect with the base of the receptor cells to dampen sounds selectively.

sensory pathway The chain of neural connections from sensory receptor cells to the cortex.

thalamus The brain regions at the top of the brainstem that trade information with the cortex.

central modulation of sensory information The process in which higher brain centers, such as the cortex and thalamus, suppress some sources of sensory information and amplify others.


(a) Experimental setup
Amplifier A
Amplifier B
Receptive field for cortical neuron A
Receptive field for cortical neuron B
Forelimb
Tail
(b) Cortical cell with receptive field on forelimb
Period of stimulation
Cortical neuron A
Touch outside of receptive field has no effect (spontaneous activity).
Touch in center of receptive field excites.
Touch in surround inhibits.
(c) Cortical cell with receptive field on tail
Period of stimulation
Cortical neuron B
Touch outside of receptive field has no effect.
Touch in center of receptive field excites.
Touch in surround inhibits.

8.9 Identifying Somatosensory Receptive Fields The procedures illustrated here are used to record from somatosensory neurons of the cerebral cortex. Changes in the position of the stimulus affect the rate of neural impulses. Neuron A responds to touch on a region of the forepaw; neuron B, only a few centimeters away in the somatosensory cortex, responds to stimulation of the tail. The receptive fields of these neurons include an excitatory center and an inhibitory surround, but other neurons have receptive fields with the reverse organization: inhibitory centers and excitatory surrounds.

Receptive fields: What turns on this particular receptor cell?

The **receptive field** of a sensory neuron consists of a region of space in which a stimulus will alter the neuron's firing rate. To determine this receptive field, investigators record the neuron's electrical responses to a variety of stimuli to see what makes the activity of the cell change from its resting rate (**Figure 8.9**). For example, which patch of skin must we vibrate to change the activity of a particular Pacinian corpuscle? Such experiments show that somatosensory receptive fields have either an excitatory center and an inhibitory surround, or an inhibitory center and an excitatory surround. These receptive fields make it easier to detect edges and discontinuities on the objects we feel.

Receptive fields differ also in size and shape, and in the quality of stimulation that activates them. For example, some neurons respond preferentially to light touch, while others fire most rapidly in response to painful stimuli, and still others respond to cooling.

Following sensory information from the receptor cell in the periphery into the brain shows that neurons all along the pathway will respond to particular stimuli, so each of these cells has a receptive field. But as each successive neuron combines information from prior cells in the pathway, the receptive fields change considerably. Receptive fields have been studied for cells at all levels, from the periphery to the brain, and we will see many examples of receptive fields later in this chapter and in the next two chapters.

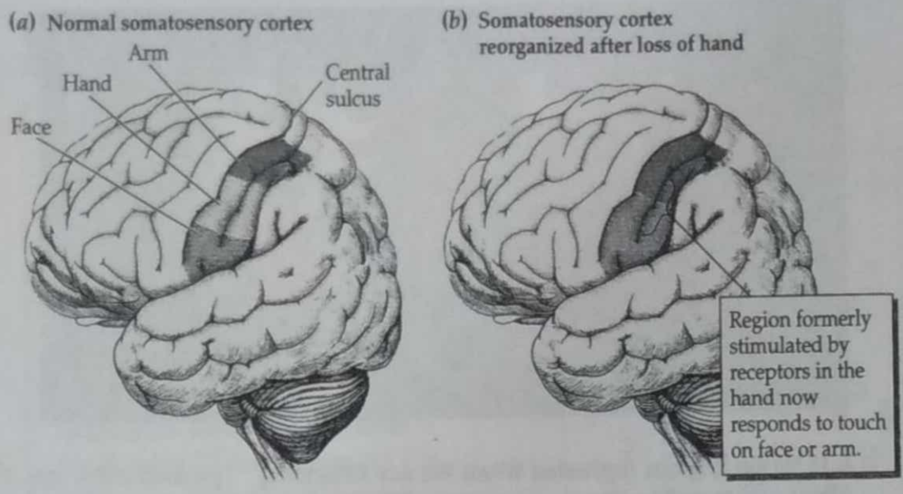
RECEPTIVE FIELDS IN THE CEREBRAL CORTEX For a given sensory modality we can find several different regions of cortex that receive information about that sense. Each of these cortical regions has a separate map of the same receptive surface, but the different cortical regions process the information differently and make different contributions to perceptual experiences (Miyashita, 1993; Zeki, 1993).

By convention, one of the cortical maps is designated as **primary sensory cortex** for that particular modality. Thus there is primary somatosensory cortex, primary auditory cortex, and so on. The other cortical maps for a given modality are said to be **secondary sensory cortex**, or **nonprimary sensory cortex** (see Figure 8.8). The primary cortical area is the main source of input to the other fields for the same modality, even though these

receptive field The stimulus region and features that cause the maximal response of a cell in a sensory system.

primary sensory cortex For a given sensory modality, the region of cortex that receives most of the information about that modality from the thalamus or, in the case of olfaction, directly from the secondary sensory neurons.

secondary sensory cortex or nonprimary sensory cortex For a given sensory modality, the cortical regions receiving direct projections from primary sensory cortex for that modality.


(a) Normal somatosensory cortex
Arm
Hand
Face
Central sulcus
(b) Somatosensory cortex reorganized after loss of hand
Region formerly stimulated by receptors in the hand now responds to touch on face or arm.

8.10 Normal and Reorganized Somatosensory Cortex (a) Primary somatosensory cortex (S1) lies in a strip just behind the central sulcus. Normally the cortical region receiving information from the hand is interposed between the regions representing the upper arm and the face. We can map these receptive fields in animals by stimulating the body to see which skin regions activate various parts of S1. In humans we can map S1 using functional brain imaging to determine which skin regions activate various parts of S1. (*b*) In a person who, as an adult, lost one hand, the cortical regions representing the upper arm and face expand, taking over the cortical region previously representing the missing hand. Presumably the loss of sensory input from the lost hand allows those cortical neurons to become innervated by neighboring cortical neurons. (After Yang et al., 1994.)

other fields also have direct thalamic inputs. Information is sent back and forth between the primary and nonprimary sensory cortex through subcortical loops.

Primary somatosensory cortex of each hemisphere—known as **somatosensory 1** or **S1** (**Figure 8.10a**)—receives touch information from the opposite side of the body. **Secondary somatosensory cortex** (**somatosensory 2**, or **S2**) maps both sides of the body in registered overlay; that is, the left-arm and right-arm representations occupy the same part of the map, and so forth.

Attention: How do we notice some stimuli but not others?

In 1890, William James wrote, "Everyone knows what attention is. It is the taking possession by the mind in clear and vivid form one out of what seem several simultaneous objects or trains of thought." In fact, however, not everyone agrees about the definition of **attention**. This important aspect of sensory processing has a multiplicity of meanings.

One view emphasizes the state of alertness or vigilance that enables animals to detect signals. In this view, attention is a generalized activation that attunes us to all inputs. According to another view, attention is the process that allows the *selection* of some sensory inputs from among many competing ones. Other investigators view attention as a "mental spotlight" that focuses on some stimuli, casting others in a "shadow." Obviously this "self-evident" notion has considerable complexity.

Certain regions of the cerebral cortex have been particularly implicated in attention because damage to those places impairs attention in people and animals. In addition, electrical activity of neurons in these regions is altered when animals attend to stimuli or await stimuli in order to obtain rewards.

One cortical region that appears to play a special role in attention is a part of the posterior parietal lobe. Many cells here are especially responsive in a trained monkey that is expecting the appearance of a stimulus (Mountcastle et al., 1981), whether auditory or visual. Lesions of this area in monkeys result in inattention or neglect of stimuli on the opposite side. (In Chapter 19 we will see that this symptom is especially severe in people with lesions of the right parietal lobe.) A portion of the frontal cortex, called the *frontal eye fields*, seems to be involved in attentive visual exploration of space. The *cingulate cortex* (the portion of cortex along and just above the corpus callosum; see Figure 2.15) has been implicated in motivational aspects of attention. **Figure 8.11** shows activation in the cingulate cortex during a task involving a shift in spatial orientation (Gitelman et al., 1996; Nobre et al., 1997).

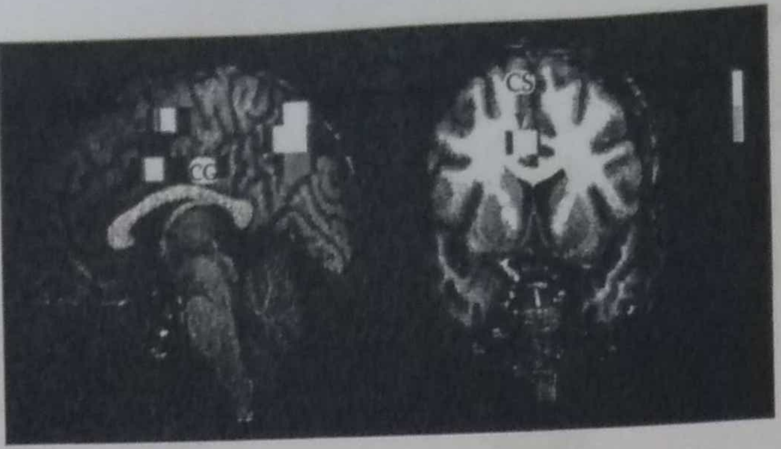
Sensory systems influence one another

Often the use of one sensory system influences perception derived from another sensory system. For example, cats may not respond to birds unless they can both see and hear the birds; neither sense alone is sufficient to elicit a response (B. Stein and Mered-

primary somatosensory cortex (S1) or somatosensory 1 The gyrus posterior to the central sulcus where sensory receptors on the body surface are mapped. Primary cortex for receiving touch and pain information, in the parietal lobe.

secondary somatosensory cortex (S2) or somatosensory 2 The region of cortex that receives direct projections from primary somatosensory cortex.

attention A state or condition of selective awareness or perceptual receptivity, possibly involving the activation of certain brain regions.



8.11 Brain Regions Activated When We Are Attending Functional-MRI images of a subject cued to expect a stimulus in a particular portion of the visual field show right-hemisphere activation in the cingulate cortex in midsagittal (*left*) and frontal (*right*) views. Areas of highest activation are shown in yellow. CG, cingulate gyrus; CS, cingulate sulcus. (Courtesy of Darren Gitelman.)

ith, 1993). Similarly, humans detect a visual signal more accurately if it is accompanied by a sound from the same part of space (McDonald et al., 2000).

Many sensory areas in the brain—so-called *association areas*—do not represent exclusively a single modality, but show a mixture of inputs from different modalities. Some "visual" cells, for instance, also respond to auditory or touch stimuli. Perhaps loss of input from one modality allows these cells to analyze input from the remaining senses better, as happens, for example, in cases of people who become blind early in life and are better than sighted people at localizing auditory stimuli (Gougoux et al., 2005). The normal stimulus convergence on such **polymodal** cells provides a mechanism for intersensory interactions (Fuster et al., 2000). For a few people, stimulus in one modality may evoke an additional perception in another modality, as when seeing a number evokes a color, or hearing different tones evokes different flavors—a situation that is described further in **Box 8.1**.

Touch: Many Sensations Blended Together

The skin that envelops our bodies is a delicate yet durable boundary that separates us from our surroundings. It also presents to the world a massive array of sensory receptors monitoring many types of stimuli. Among primates, an important aspect of skin sensations is the active manipulation of objects by the hands, which enables the identification of various shapes.

But touch is not just touch. Careful studies of skin sensations reveal qualitatively different sensory experiences: pressure, vibration, tickle, "pins and needles," and more-complex dimensions, such as smoothness or wetness—all recorded by the receptors in the skin.

Skin Is a Complex Organ That Contains a Variety of Sensory Receptors

Because the average person has about 1 to 2 m^2 (10 to 20 square feet) of skin, skin is sometimes considered the largest human organ. Skin is made up of three separate layers; the relative thickness of each varies over the body surface. The outermost layer—the **epidermis**—is the thinnest. The middle layer—the **dermis**—contains a rich web of nerve fibers in a network of connective tissue and blood vessels. The innermost layer—the **hypodermis**—provides an anchor for muscles, contains Pacinian corpuscles, and helps shape the body.

polymodal Involving several sensory modalities.

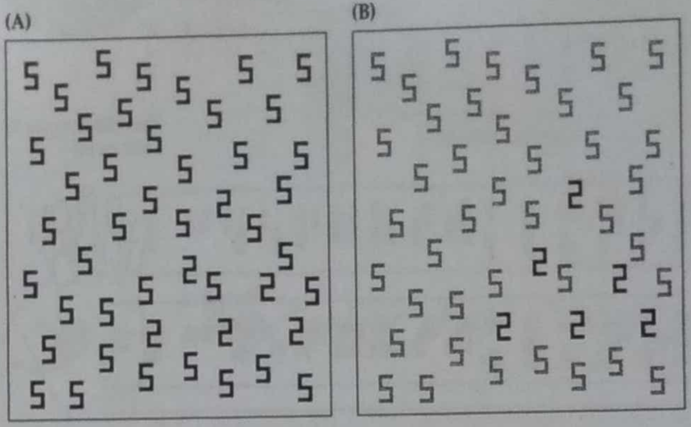
epidermis The outermost layer of skin, over the dermis.

dermis The middle layer of skin, between the epidermis and the hypodermis.

hypodermis The innermost layer of skin, under the dermis.

BOX 8.1 Synesthesia

For a few people, stimuli in one modality evoke the involuntary experience of an additional sensation in another modality—a condition known as **synesthesia** (from the Greek *syn*, "union," and *aesthesis*, "sensation"). For example, a person with synesthesia (a "synesthete") may perceive different colors when seeing different letters of the alphabet ("D looks green, but E is red") or words for days of the week ("Tuesday is a yellow word"). In another example, a musician experienced a particular taste whenever she heard a specific musical tone interval (Beeli et al., 2005). Discordant tones evoked unpleasant tastes. How common synesthesia is depends to some extent on how it's defined, but it is estimated that as much as 2% to 4% of the population displays some form of synesthesia, and as much as 1% reports experiencing a color with particular letters or numbers (Simner et al., 2006). Synesthesia is more commonly reported among artists and poets than in the general population, so synesthesia may be associated with creativity.



Since you probably do not have this experience, you may doubt whether other people really do, if the basis for knowing that they do is self-report alone. For some forms of synesthesia, however, a clever test may confirm whether, for example, "2 is red but 5 is green." To someone who reported having this experience, Ramachandran and Hubbard (2001) showed a page like that in Figure A and asked the person to quickly point to all of the 2s. Because the shapes of 2 and 5 are so similar, it takes a certain amount of time for most people to pick out each 2 among all those 5s, but this subject found them much faster than that. For such a synesthete, the numbers look colored, as in Figure B; and with the addition of colors, it's certainly much easier to pick out the 2s.

If you are interested in probing whether you share this experience, Eagleman et al. (2007) have posted a collection of tests for synesthesia online at http://synesthete.org.

synesthesia A condition in which stimuli in one modality evoke the involuntary experience of an additional sensation in another modality.

Pain, heat, and cold at the skin are detected by free nerve endings (see Figure 8.4), which are described later in this chapter. In contrast, light touch is detected by four highly sensitive touch receptors (**Figure 8.12**). We mentioned earlier the Pacinian corpuscles, which are found deep within the dermis. The onionlike outer portion of the corpuscle acts as a filter, shielding the underlying nerve fiber from most stimulation. Only vibrating stimuli of more than 200 Hz will pass through the corpuscle and stretch the nerve fiber to reach threshold. Normally the skin receives this sort of rapid vibration when it is moving across the textured surface of an object. Pacinian corpuscles are fast-responding and fast-adapting receptors (**Figure 8.12*a***).

The **tactile** (touch) receptors that mediate most of our ability to perceive form are the fast-adapting **Meissner's corpuscles** (**Figure 8.12*b***) and the slow-adapting, oval **Merkel's discs** (**Figure 8.12*c***). These receptors are especially densely distributed in skin regions where sensitive spatial discrimination is possible (fingertips, tongue, and lips).

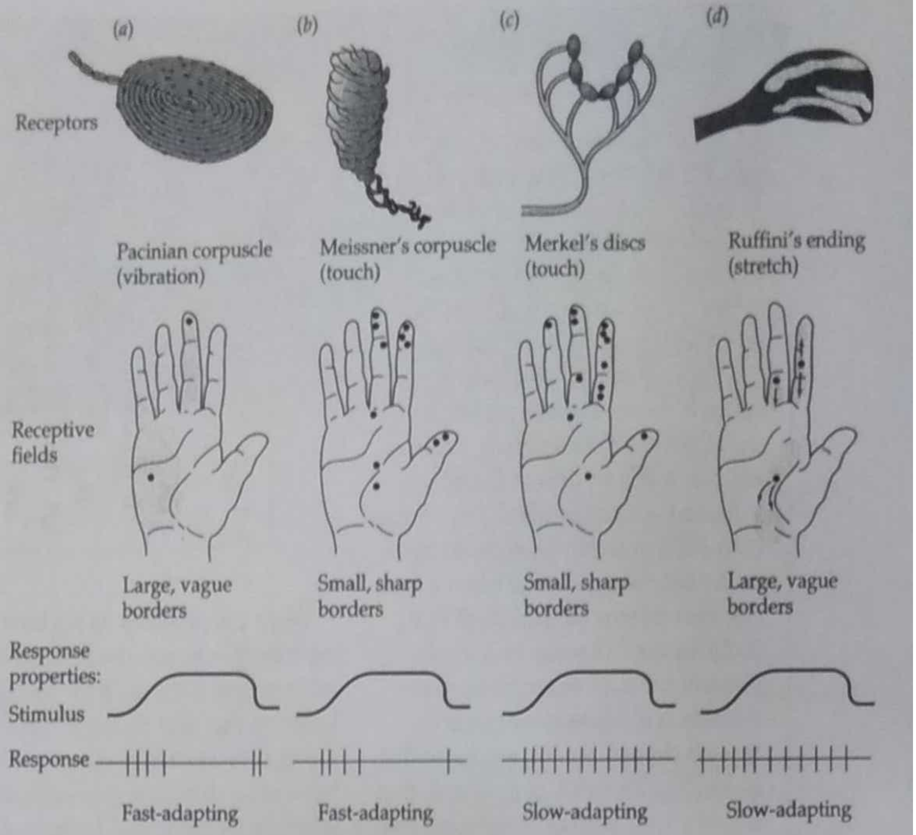
The receptive fields of Merkel's discs usually have an inhibitory surround, which increases their spatial resolution. This field also makes them especially responsive to edges and to isolated points on a surface (such as the dots for Braille characters).

Meissner's corpuscles are more numerous than Merkel's discs but offer less spatial resolution. Meissner's corpuscles seem specialized to respond to *changes* in stimuli (as one would expect from rapidly adapting receptors) to detect localized movement between the skin and a surface. This sensitivity to change in stimuli provides detailed in-

tactile Of or relating to touch.

Meissner's corpuscle A skin receptor c type that detects light touch.

Merkel's disc A skin receptor cell type t detects light touch.


(a)
(b)
(c)
(d)
Receptors
Pacinian corpuscle (vibration)
Meissner's corpuscle (touch)
Merkel's discs (touch)
Ruffini's ending (stretch)
Receptive fields
Large, vague borders
Small, sharp borders
Small, sharp borders
Large, vague borders
Response properties:
Stimulus
Response
Fast-adapting
Fast-adapting
Slow-adapting
Slow-adapting

8.12 Properties of Skin Receptors Related to Touch Shown here for each skin receptor is the type of receptor (*top*), the size and type of the receptive field (*middle*), and the electrophysiological response (*bottom*). (*a*) Pacinian corpuscles activate fast-adapting fibers with large receptive fields. (*b*) Meissner's corpuscles are fast-adapting mechanoreceptors with small receptive fields. (*c*) Merkel's discs are slow-adapting receptors with small receptive fields. (*d*) Ruffini's endings are slow-adapting receptors with large receptive fields. (After Valbo and Johansson, 1984.)

formation about texture (K. O. Johnson and Hsiao, 1992). The low-threshold, rapidly adapting characteristics of Meissner's corpuscles may be due to a specialized Na^+ channel (M. P. Price et al., 2000).

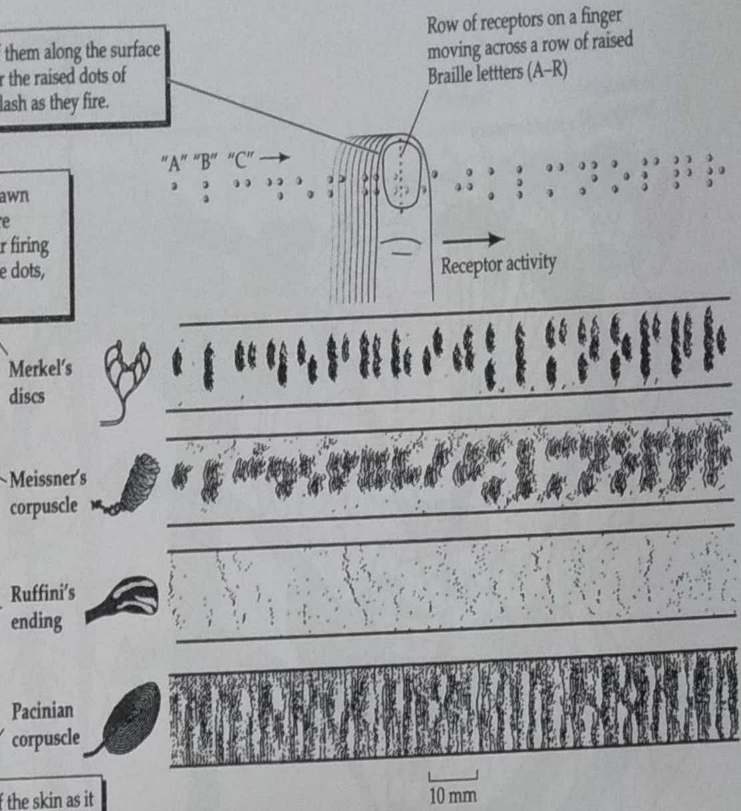
The final touch receptors are the slow-adapting **Ruffini's endings**, which detect stretching of the skin when we move fingers or limbs (**Figure 8.12*d***). There are very few Ruffini's endings (Pare et al., 2003).

Figure 8.13 compares how the four touch receptors respond when a finger is moved across the raised dots of Braille. All four of these light-touch receptors utilize moderately large (so-called Aβ) myelinated fibers (**Table 8.2**). Recall from Chapter 3 that large axons conduct action potentials faster than small axons, and that myelination speeds conduction even more. So the light-touch receptors send information very rapidly to the CNS. Later in this chapter we'll learn that some pain fibers conduct rapidly while others conduct slowly. In Chapter 11 we'll meet a man whose large fibers were destroyed by a virus, so he can no longer feel light touch. He can still feel pain, coolness, and warmth on his skin because those smaller axons were spared.

The Dorsal Column System Carries Somatosensory Information from the Skin to the Brain

Later we will describe the spinothalamic system that carries information about pain and temperature. The discussion here will focus on the system that gathers information about touch. The touch receptors that we have described (Pacinian corpuscles, Merkel's

Ruffini's ending A skin receptor cell type that detects stretching of the skin.



Your skin is full of receptors. Consider a row of them along the surface of your fingertip. As you move your finger over the raised dots of Braille encoding the letters A–R, the receptors flash as they fire.

Merkel's discs fire only when they are being drawn over the dot and, because they adapt slowly, fire continuously while passing over each dot. Their firing pattern produces a faithful representation of the dots, providing form information.

Meissner's corpuscles have larger receptive fields, so their activity does not distinguish the various Braille letters as well as Merkel's discs do. Meissner's corpuscles also adapt quickly, so they slow down while passing over each dot.

Ruffini's endings respond to stretch, so they fire as the skin is stretched while passing over the raised dots, but they don't provide a complete representation of form. They adapt slowly to stretch.

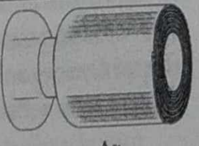
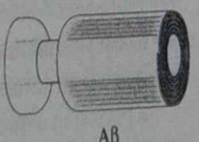
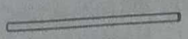
Pacinian corpuscles respond to the vibration of the skin as it rubs the paper surface, providing information about texture. They fire less while passing over the dots, perhaps because the dots dampen local vibration as they pass. This vibration sensitivity provides useful information about the response of any tool being used by the hand.

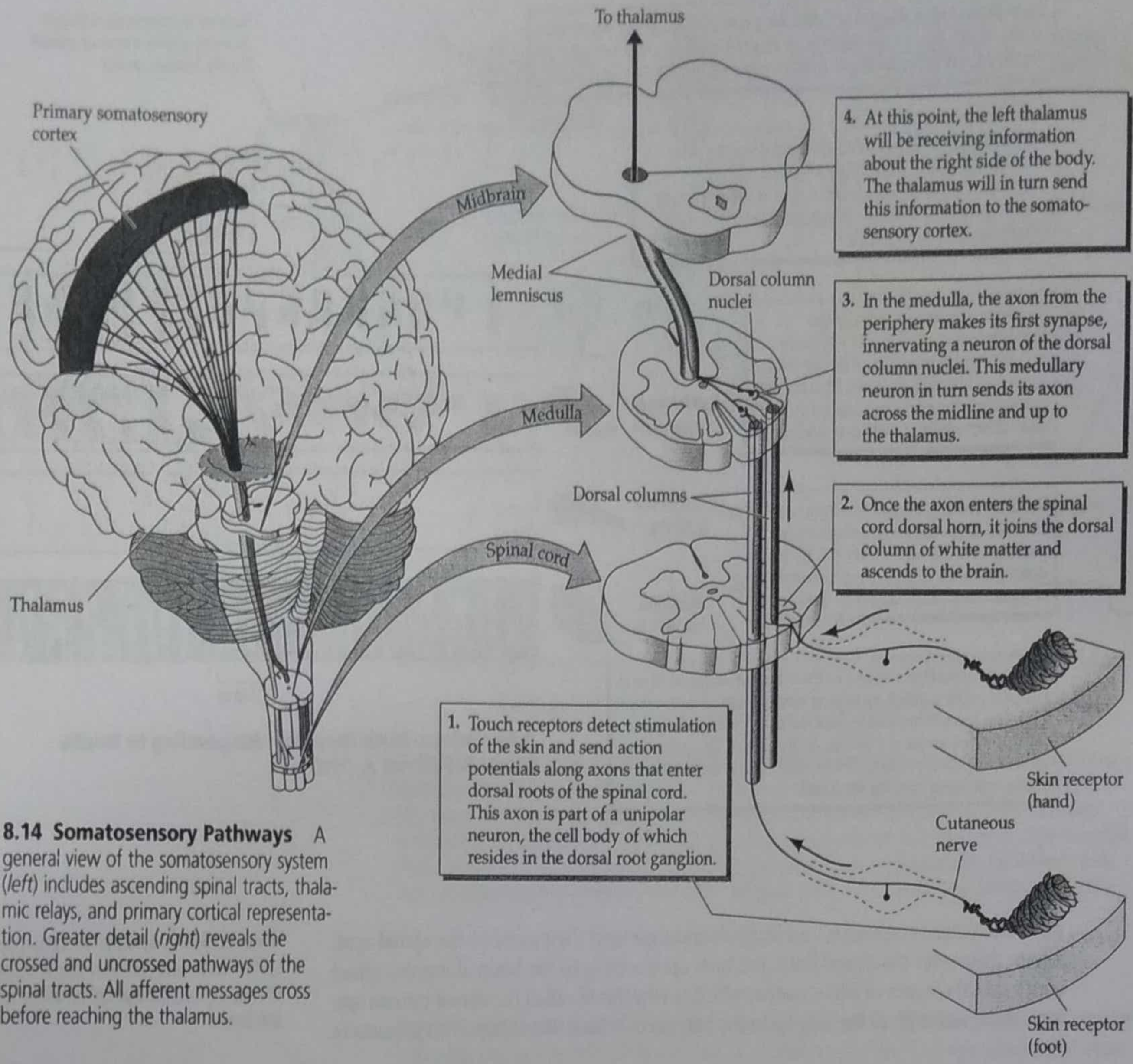
8.13 Various Touch Receptors Responding to Braille
(After J. R. Phillips et al., 1990.)

discs, Meissner's corpuscles, and Ruffini's endings) send their axons to the spinal cord, where they enter the dorsal horn and turn up, traveling to the brain along the spinal cord's dorsal column of white matter, which is why this is called the **dorsal column system**. These axons go all the way up to the brainstem, where they synapse on neurons of

dorsal column system A somatosensory system that delivers most touch stimuli via the dorsal columns of spinal white matter to the brain.

TABLE 8.2 Fibers That Link Receptors to the CNS

Sensory function(s)	Receptor type(s)	Axon type	Diameter (μm)	Conduction speed (m/s)
Proprioception (see Chapter 11)	Muscle spindle	 Aα	13–20	80–120
Touch (see Figures 8.12 and 8.13)	Pacinian corpuscle, Ruffini's ending, Merkel's disc, Meissner's corpuscle	 Aβ	6–12	35–75
Pain, temperature	Free nerve endings; TRP2	Aδ	1–5	5–30
Temperature, pain, itch	Free nerve endings; TRPV1, CMR1	 C	0.02–1.5	0.5–2



4. At this point, the left thalamus will be receiving information about the right side of the body. The thalamus will in turn send this information to the somatosensory cortex.

3. In the medulla, the axon from the periphery makes its first synapse, innervating a neuron of the dorsal column nuclei. This medullary neuron in turn sends its axon across the midline and up to the thalamus.

2. Once the axon enters the spinal cord dorsal horn, it joins the dorsal column of white matter and ascends to the brain.

1. Touch receptors detect stimulation of the skin and send action potentials along axons that enter dorsal roots of the spinal cord. This axon is part of a unipolar neuron, the cell body of which resides in the dorsal root ganglion.

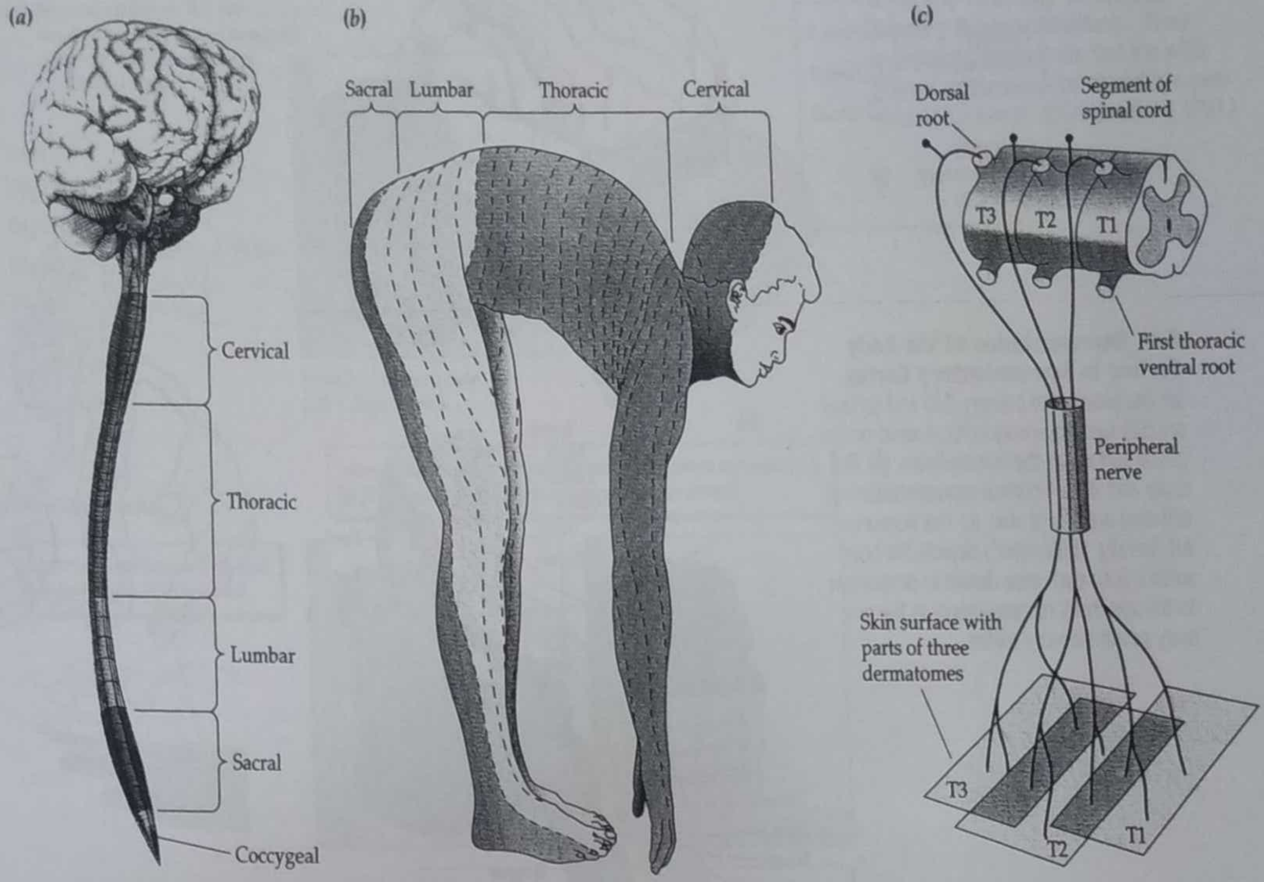
8.14 Somatosensory Pathways A general view of the somatosensory system (*left*) includes ascending spinal tracts, thalamic relays, and primary cortical representation. Greater detail (*right*) reveals the crossed and uncrossed pathways of the spinal tracts. All afferent messages cross before reaching the thalamus.

the dorsal column nuclei in the medulla (**Figure 8.14**). The axons of these medullary neurons then cross the midline to the opposite side and ascend to a group of nuclei of the thalamus. Outputs of the thalamus are directed to postcentral cortical regions referred to as the *somatosensory cortex* or *S1*.

The skin surface can be divided into bands called *dermatomes* according to which spinal nerve carries the axons from each region (**Figure 8.15*a***). A **dermatome** (from the Greek *derma*, "skin," and *tome*, "part" or "segment") is a strip of skin innervated by a particular spinal root. The pattern of dermatomes is hard to understand in an upright human, but remember that erect posture is a recent evolutionary development in mammals. The mammalian dermatomal pattern evolved among our quadrupedal (four-legged) ancestors. Thus the dermatomal pattern makes more sense when depicted on a person in a quadrupedal posture (**Figure 8.15*b***). The dermatomes overlap a modest amount (**Figure 8.15*c***).

The cells in all brain regions concerned with somatic sensation are arranged according to the plan of the body surface. Each region is a map of the body in which the relative areas devoted to body regions reflect the density of body innervation. Because many fibers are involved with the sensory surface of the head, especially the lips, a particularly

dermatome A strip of skin innervated by a particular spinal root.



8.15 Dermatomes (*a*) Bands of skin send their sensory inputs to different dorsal roots of the spinal cord. Each dermatome is the section of the skin that is innervated primarily by a given dorsal root of the spinal cord. (*b*) In this side view of the human body in quadrupedal position, the pattern of dermatomes is color-coded to correspond to the spinal regions in a, and it appears more straightforward than it would in the erect posture. (*c*) Adjacent dorsal roots of the spinal cord collect sensory fibers from overlapping strips of skin, so the boundaries between the dermatomes overlap.

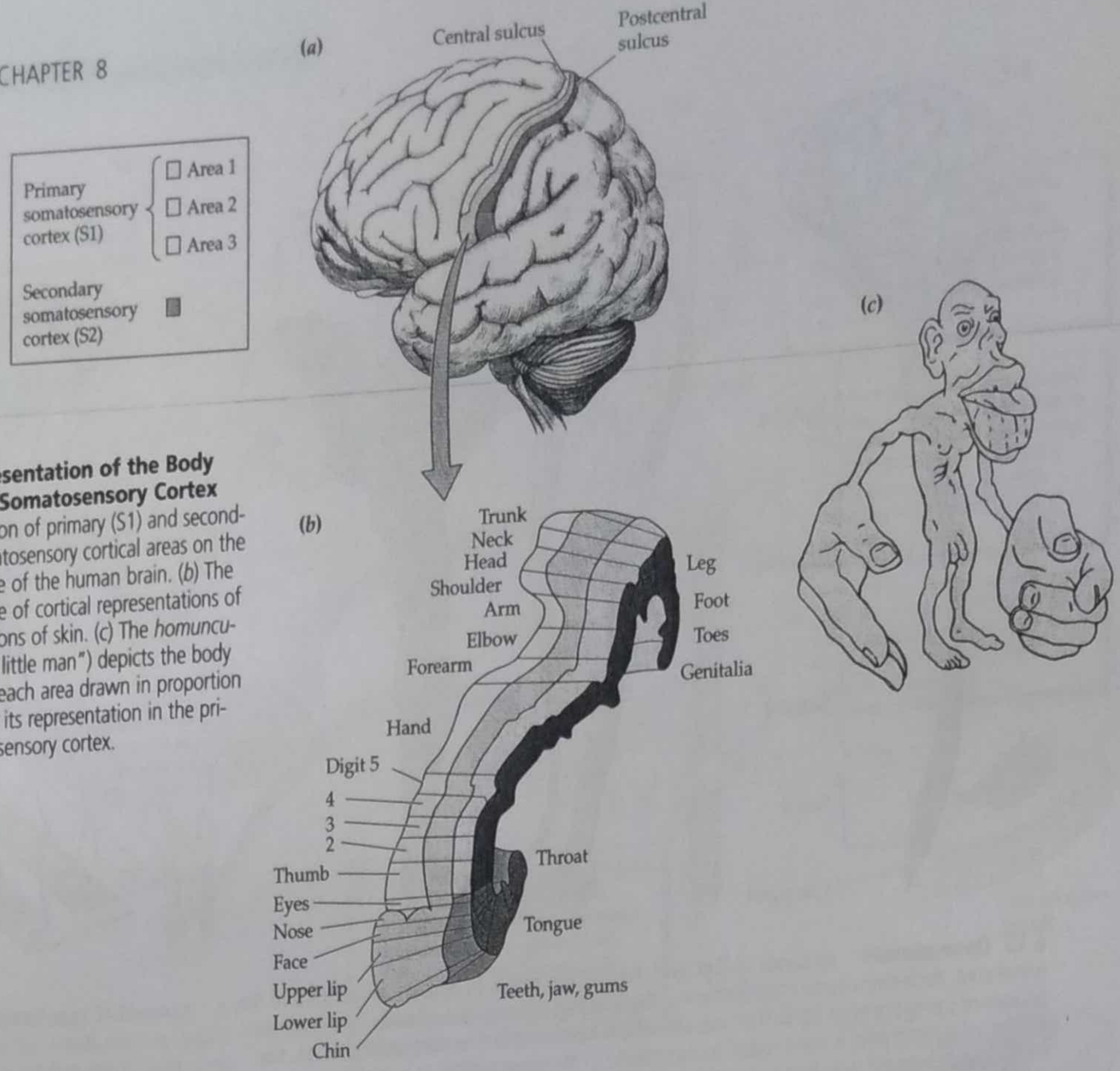
large number of cells are concerned with the head; in contrast, far fewer fibers innervate the trunk, so the number of cortical cells that represent the trunk is much smaller (**Figure 8.16**).

Some mammals have a very different pattern of representation in somatosensory cortex. For example, the nose of the star-nosed mole is a very sensitive organ for touch, and a considerable portion of its somatosensory cortex is devoted to responding to each of the 11 rays of the "star" (**Figure 8.17**) (Catania, 2001). For information about the organization of sensory information within a column of somatosensory cortex, see **A Step Further: Cortical Columns Show Specificity for Modality and Location** on the website.

Plasticity in cortical maps: Receptive fields can be changed by experience

At one time most researchers thought that cortical maps were fixed early in life and were invariant among all members of the same species. Now, however, we know that cortical maps can change with experience (Merzenich and Jenkins, 1993).

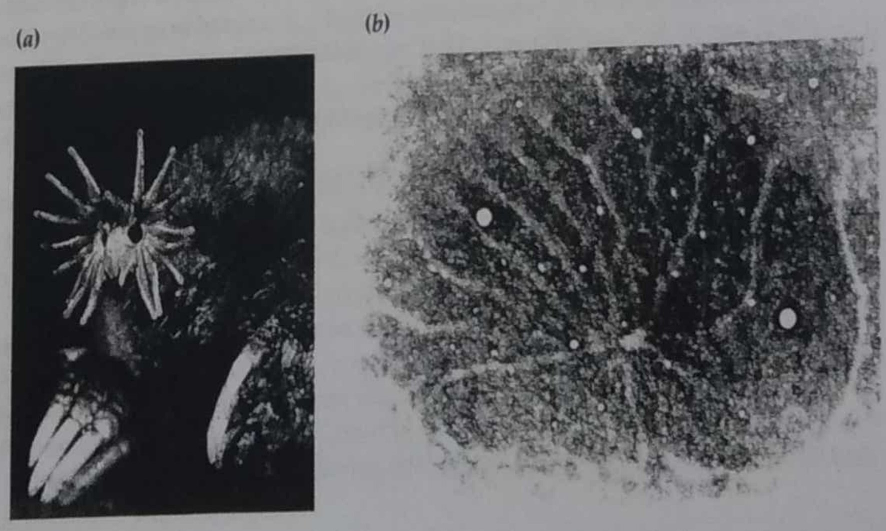
In one experiment, the receptive field of a monkey's hand was mapped in detail in the somatosensory cortex (**Figure 8.18*a***). Then the nerve to the thumb and index finger was severed. After a few weeks, remapping the same somatosensory cortex revealed that the area representing those fingers had shrunk, and stimulating the back of the hand activated the territory formerly held by the denervated fingers (**Figure 8.18*b***).


(a)
Central sulcus
Postcentral sulcus
Primary somatosensory cortex (S1)
☐ Area 1
☐ Area 2
☐ Area 3
Secondary somatosensory cortex (S2) ▨
(b)
Trunk
Neck
Head
Shoulder
Arm
Elbow
Forearm
Hand
Digit 5
4
3
2
Thumb
Eyes
Nose
Face
Upper lip
Lower lip
Chin
Leg
Foot
Toes
Genitalia
Throat
Tongue
Teeth, jaw, gums
(c)

8.16 Representation of the Body Surface in Somatosensory Cortex (a) The location of primary (S1) and secondary (S2) somatosensory cortical areas on the lateral surface of the human brain. (*b*) The order and size of cortical representations of different regions of skin. (c) The *homunculus* (literally, "little man") depicts the body surface with each area drawn in proportion to the size of its representation in the primary somatosensory cortex.

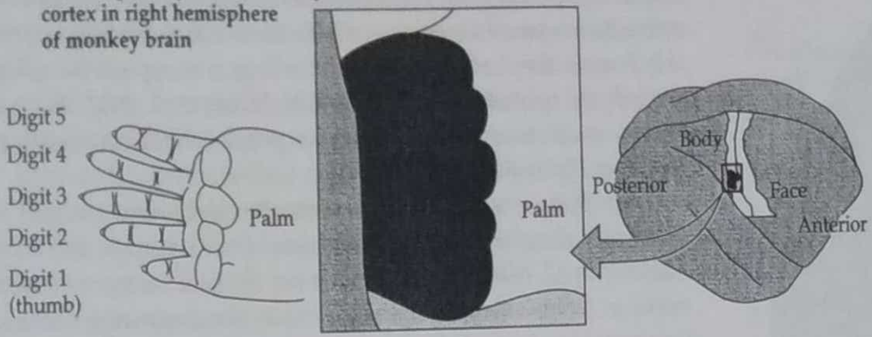
In another experiment, the middle finger was surgically removed. This treatment expanded the cortical representation of each adjacent finger (**Figure 8.18*c***).

In a third experiment, the monkey was trained to rest two fingers on a rotating disk in order to obtain food rewards. After several weeks of training, the hand area was mapped again, and the stimulated fingers were found to have considerably enlarged representations compared to their previous areas (**Figure 8.18*d***).



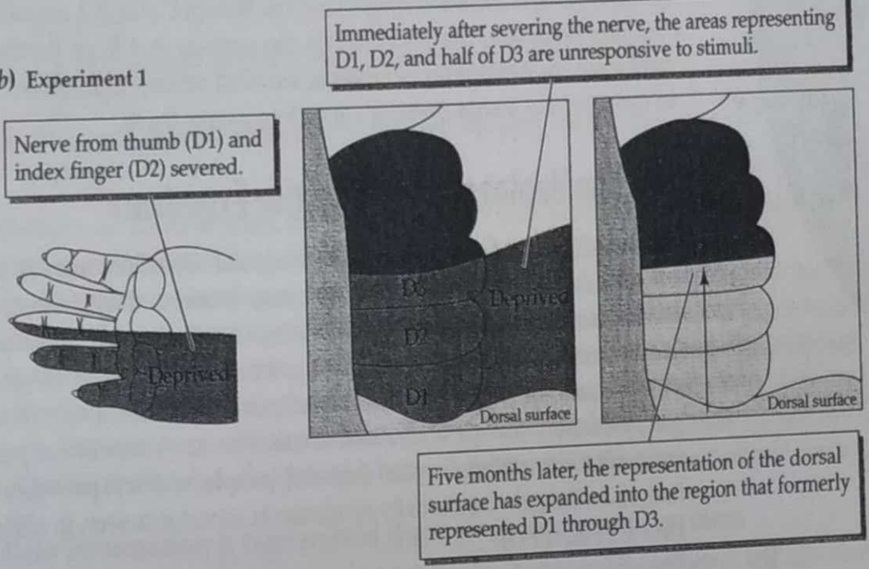
8.17 Hey There, You with the Star on Your Nose (a) The tip of the star-nosed mole's nose is a very delicate organ for touch. (*b*) In this section from the somatosensory cortex of a star-nosed mole, we can see how each of the 11 rays from one-half of the star-shaped nose projects to its own patch of cortex. The two bottommost rays, which are the most sensitive, each innervate a larger piece of cortex than the other rays. (From Catania, 2001; photographs courtesy of Ken Catania.)

(*a*) Representation of the left hand in primary somatosensory cortex in right hemisphere of monkey brain


Digit 5
Digit 4
Digit 3
Digit 2
Digit 1
(thumb)
Palm
Palm
Body
Posterior
Face
Anterior

Details of cortical map (D5 = digit 5, etc.)

(*b*) Experiment 1

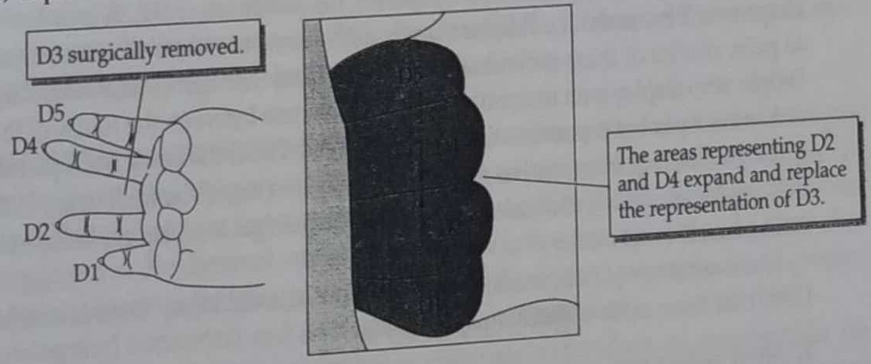

Deprived
D3
Deprived
D2
D1
Dorsal surface
Dorsal surface

Nerve from thumb (D1) and index finger (D2) severed.

Immediately after severing the nerve, the areas representing D1, D2, and half of D3 are unresponsive to stimuli.

Five months later, the representation of the dorsal surface has expanded into the region that formerly represented D1 through D3.

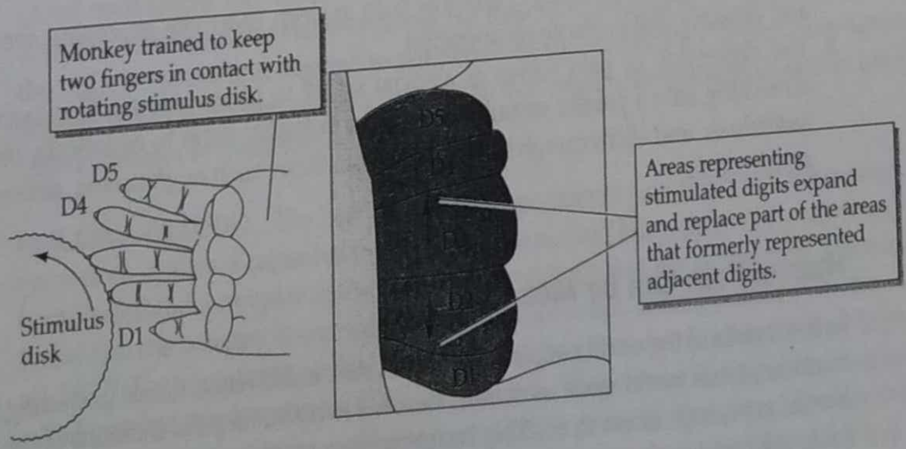
(*c*) Experiment 2



D3 surgically removed.

The areas representing D2 and D4 expand and replace the representation of D3.

(*d*) Experiment 3


D5
D4
D1
Stimulus disk

Monkey trained to keep two fingers in contact with rotating stimulus disk.

Areas representing stimulated digits expand and replace part of the areas that formerly represented adjacent digits.

8.18 The Plasticity of Somatosensory Representations These experiments demonstrate that the adult brain of monkeys can be altered by experience. (After Merzenich and Jenkins, 1993.)

Similar findings were noted in rats exposed to differential tactile experiences (Xerri et al., 1996). Professional musicians who play stringed instruments have expanded cortical representations of their left fingers, presumably because they have been using these fingers to depress the strings for precisely the right note (Elbert et al., 1995; Münte et al., 2002). Brain imaging also reveals cortical reorganization in people who lose a hand in adulthood (see Figure 8.10*b*).

Some changes in cortical maps occur after weeks or months of use or disuse; they may arise from the production of new synapses and dendrites (Florence et al., 1998; Hickmott and Steen, 2005) or the loss of others. On the other hand, some changes are so rapid, occurring within hours, that they probably arise from changes in the strength of existing synapses. Rapid changes in cortical maps may also result from a loss of sustained inhibition of some synapses; these changes could be thought of as the unmasking of "hidden synapses." As described on the website in **A Step Further: Somatosensory Perception of Objects**, we must actively manipulate objects in order for the somatosensory cortex to perceive them.

THE HUMAN PINCUSHION WHO INCURS CONSTANT RISKS OF BLOOD POISONING.

8.19 Doesn't That Hurt? The earliest scientific report of a person with congenital insensitivity to pain was of a man working in the theater, like the man shown here, as a "human pincushion." (Photograph by Culver Pictures, Inc.)

Pain: An Unpleasant but Adaptive Experience

The International Association for the Study of Pain defines **pain** as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Because pain is unpleasant and causes great suffering, it may be difficult to imagine a biological role for it. But clues to the adaptive significance of pain can be gleaned from the study of rare individuals who never experience pain. The **congenital insensitivity to pain** that such people exhibit is probably inherited, since the pain insensitivity syndrome is sometimes seen in siblings (E. Hirsch et al., 1995).

The first clinically reported person with congenital insensitivity to pain worked on the stage as a "human pincushion" (**Figure 8.19**) (Dearborn, 1932). A little later in this chapter we'll learn about a Pakistani family with several members who were insensitive to pain; studies of these individuals provided a breakthrough in understanding pain. People who display pain insensitivity can discriminate between the touch of the point or head of a pin but experience no pain when pricked with the point. Such people show extensive scarring from injuries to fingers, hands, and legs (Manfredi et al., 1981), and they tend to die young of injuries, suggesting that pain guides adaptive behavior by signaling harm to our bodies.

The experience of pain vividly teaches us how to avoid injury. Dennis and Melzack (1983) list three more ways that pain helps us:

1. Short-lasting pain causes us to withdraw from the source, often reflexively, thus preventing further damage.
2. Long-lasting pain promotes behaviors such as sleep, inactivity, grooming, feeding, and drinking that promote recuperation.
3. The expression of pain serves as a social signal to other animals. For example, screeching after a painful stimulus signals the potential harm to genetically related individuals, and elicits caregiving behavior from them, such as grooming, defending, and feeding.

Human Pain Can Be Measured

In some parts of the world people endure, with stoic indifference, rituals (including body mutilation) that would cause most other humans to cry out in pain. Incisions of the face, hands, arms, legs, or chest; walking on hot coals; and other treatments clearly harmful to the body can be part of the ritual. Comparable experiences are also seen in more

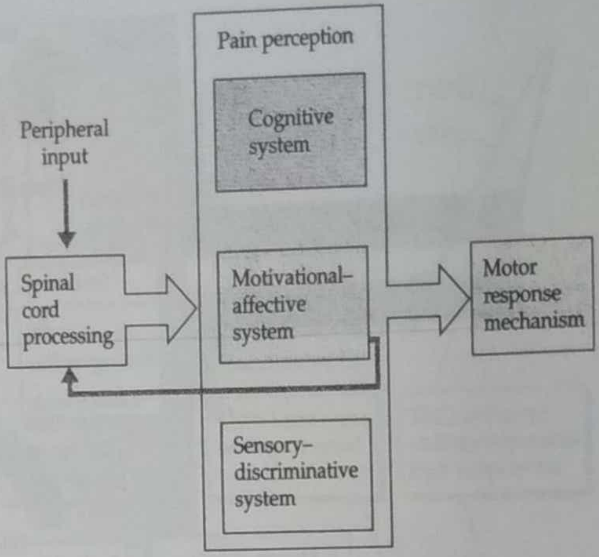
pain The discomfort normally associated with tissue damage.

congenital insensitivity to pain The condition of being born without the ability to perceive pain.

ordinary circumstances, such as when a highly excited athlete continues to play a game with a broken arm or leg. Learning, experience, emotion, and culture all affect the perception of pain in striking ways.

The mere terms *mild* and *intense* are inadequate to describe the pain that is distinctive to a particular disease or injury. Furthermore, assessment of the need for pain relief intervention requires some kind of quantitative measurement (Chapman et al., 1985). For example, Melzack (1984) has provided a detailed quantitative rating scale for pain. This rating scale—called the *McGill Pain Questionnaire*—consists of a list of words arranged into classes that describe three different aspects of pain:

1. The *sensory–discriminative* quality (e.g., throbbing, gnawing, shooting)
2. The *motivational–affective* (emotional) quality (e.g., tiring, sickening, fearful)
3. An overall *cognitive* evaluative quality (e.g., no pain, mild, excruciating).



8.20 The Multifaceted Character of Pain

Patients are asked to select the set of words that best describes their pain. These three components reflect different aspects of pain perception (**Figure 8.20**).

One of the interesting aspects of the McGill scale is that it can distinguish among pain syndromes, meaning that patients use a distinctive constellation of words to describe a particular pain experience. For example, the pain of toothache is described differently from the pain of arthritis, which in turn is described differently from menstrual pain. The simple query by a physician "Is the pain still there?" has been replaced by a more detailed analysis that provides better clues about the effectiveness of pain control.

Pain information is transmitted through special neural systems

Contemporary studies of pain mechanisms have revealed receptors in the skin that transmit pain information and have elucidated the relevant pathways in the central nervous system. In this section we will discuss some features of peripheral and central nervous system pathways that mediate pain.

PERIPHERAL ORIGINS OF PAIN INFORMATION In most cases the initial stimulus for pain is the destruction or injury of tissue adjacent to certain nerve fibers. The damaged tissue releases chemicals that activate pain fibers in the skin. Various substances have been suggested as the chemical mediators of pain, including neuropeptides, serotonin, histamine, various proteolytic (protein-metabolizing) enzymes, prostaglandins (a group of widespread hormones), and nerve growth factor (**Figure 8.21**).

It is now clear that some peripheral receptors and nerve fibers are specialized for signaling noxious stimulation. These receptors that respond to noxious stimulation are called **nociceptors**. **Free nerve endings** in the dermis display no specialized structures (they just look like naked nerve endings), but they have specialized receptor proteins on the cell membrane that respond to temperatures and chemicals. Different free nerve endings produce different receptor proteins, so they report different stimuli, such as pain and/or changes in temperature.

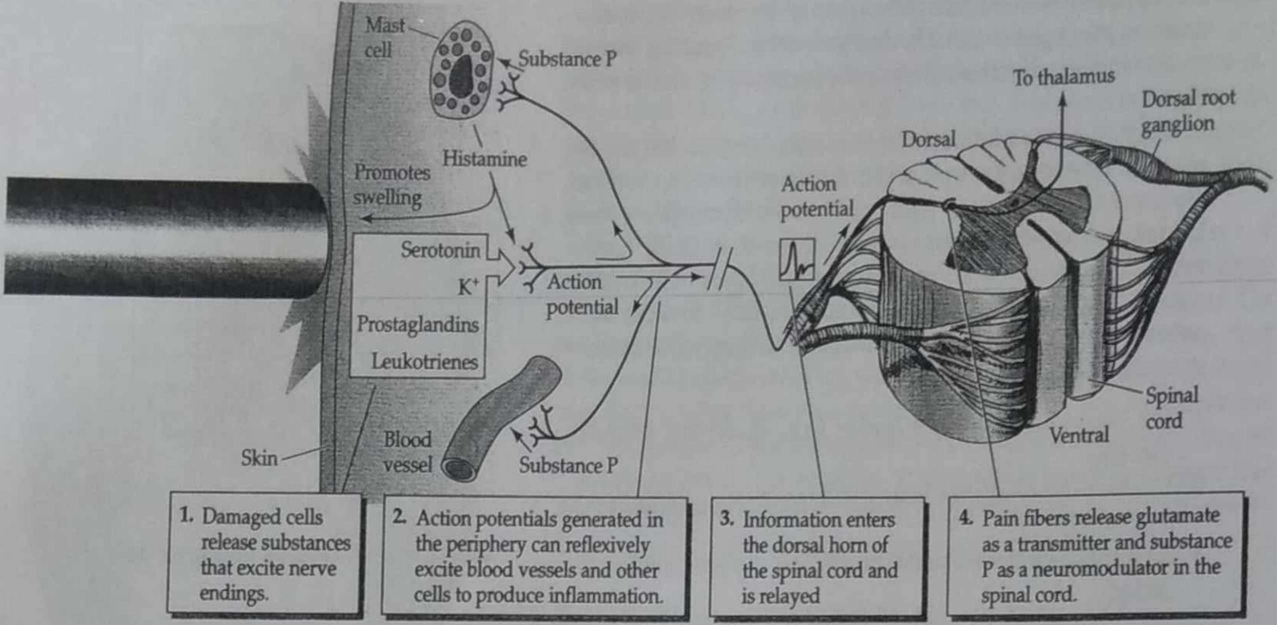
HOT, COLD, OR COOL? The best evidence for specialized pain fibers in the periphery came from studies of **capsaicin**, the chemical that makes chili peppers spicy hot. Investigators isolated a receptor found in free nerve endings that binds capsaicin, and they found that the receptor also responds to sudden increases in temperature (Caterina et al., 1997). The receptor was cloned and found to be a member of a family of proteins called *transient receptor potential* (*TRP*) ion channels. They named the capsaicin receptor **transient receptor potential vanilloid type1** (**TRPV1**), or *vanilloid receptor 1* because the crucial component of the capsaicin molecule is a chemical known as *vanilloid*. Mice lack-

nociceptor A receptor that responds to stimuli that produce tissue damage or pose the threat of damage.

free nerve ending An axon that terminates in the skin without any specialized cell associated with it and that detects pain and/or changes in temperature.

capsaicin A compound synthesized by various plants to deter predators by mimicking the experience of burning.

transient receptor potential vanilloid type 1 (TRPV1) A receptor that binds capsaicin to transmit the burning sensation from chili peppers and may detect sudden increases in temperature.



1. Damaged cells release substances that excite nerve endings.

2. Action potentials generated in the periphery can reflexively excite blood vessels and other cells to produce inflammation.

3. Information enters the dorsal horn of the spinal cord and is relayed

4. Pain fibers release glutamate as a transmitter and substance P as a neuromodulator in the spinal cord.

8.21 Peripheral Mediation of Pain When the skin is injured, activity of the peripheral nervous system causes the local release of various substances.

ing the gene for this receptor still responded to mechanosensory pain, but not to mild heat or capsaicin (Caterina et al., 2000). So the reason that chili peppers taste "hot" is that the capsaicin in the peppers activates TRPV1 receptors in the body that normally detect noxious heat. The venom of a Caribbean tarantula contains three different peptides that all activate the same receptor (Siemens et al., 2006).

TRPV1's normal job is to report a rise in temperature to warn us of danger. Chili peppers evolved the chemical capsaicin to ward off mammalian predators, as its ability to deter deer from eating prized flower bushes, which we learned about at the start of the chapter, suggests. Capsaicin molecules have the perfect shape to bind to TRPV1 and open its ion channel, just as heat normally does. Because the brain interprets action potentials from that nerve as signaling painful heat, we (and the deer) experience painful heat.

Why, though, aren't birds discouraged by capsaicin? The answer is that the *bird* version of TRPV1 is *not* affected by capsaicin (Tewksbury and Nabhan, 2001). In this case both the animal and the plant are benefited by capsaicin: the birds are able to get food from the plants—food that might be gone if mammals were able to eat it—and in the process they spread the seeds of the plants far and wide. Clever, clever chili plants.

Why do our lips swell when we have overindulged in capsaicin? As Figure 8.21 illustrates, the action potentials generated by the chemical travel back out other branches of the axon to affect blood vessels and mast cells, triggering the swelling. Paradoxically, rubbing capsaicin into the skin overlying arthritic joints brings some pain relief, perhaps because overactivated pain fibers temporarily run out of transmitter.

A related receptor, **TRP2**, detects even higher temperatures than does TRPV1 (**Figure 8.22*a***). TRP2 differs from TRPV1 in two other ways as well: TRP2 does *not* respond to capsaicin, and TRP2 receptors are found on larger nerve fibers than those carrying TRPV1. Recall from Chapter 3 that large axons conduct action potentials more rapidly than do small axons. TRP2 receptors are found on relatively large axons known as type **Aδ fibers**: large-diameter, myelinated axons (**Figure 8.22*b***). Because of the relatively large axon diameter and myelination, these fibers report to the spinal cord very quickly. When you burn your finger on a hot skillet, the first, sharp pain you feel is conducted by these fat Aδ fibers that detected the heat with TRP2 receptors. In contrast, the nerve fibers that possess TRPV1 receptors consist of thin, unmyelinated fibers called **C fibers** (see Figure 8.22*b*). These C fibers conduct slowly, and TRPV1 adapts slowly, providing the second wave of pain—the dull, lasting ache in that darned finger.

transient receptor protein 2 (TRP2) A receptor, found in some free nerve endings, that opens its channel in response to rising temperatures.

Aδ fiber A moderately large, myelinated, and therefore fast-conducting, axon, usually transmitting pain information.

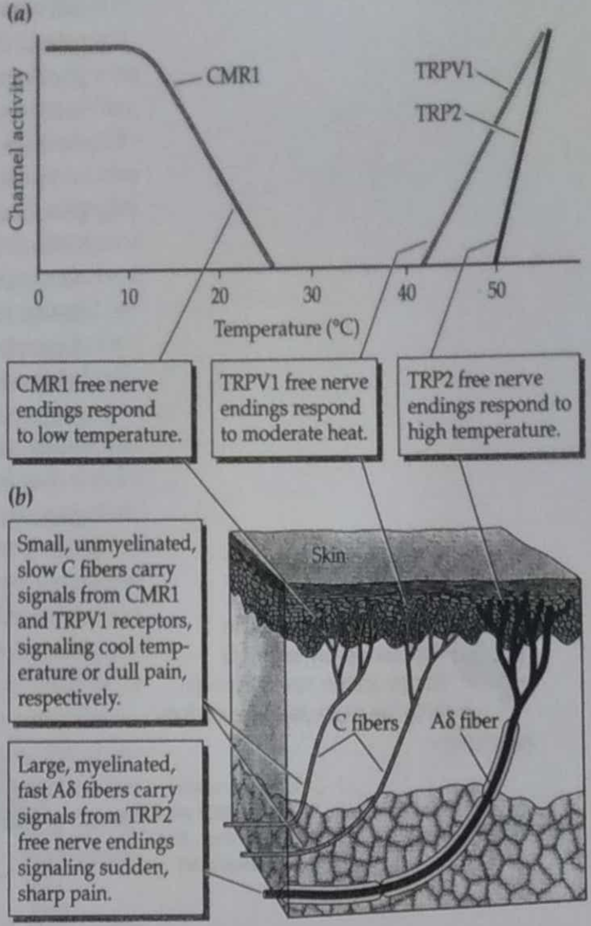
C fiber A small, unmyelinated axon that conducts pain information slowly and adapts slowly.

Why is there a slight delay between licking the cut surface of a chili pepper and feeling the burn? The reason is that only the TRPV1 fibers, with their slow conduction velocity, have been activated, not the fast Aδ fibers using TRP2. The free nerve endings that signal itch form another important class of signals from the skin that use slow C fibers (Andrew and Craig, 2001). These itch fibers respond to histamine released by mast cells near an injury (see Figure 8.21). Table 8.2 compares these different fibers.

Taking a cue from the success with capsaicin, another group of investigators tried looking for the "coolness" receptor, reasoning that it should respond to the chemical menthol. They found and named **cool-menthol receptor 1** (**CMR1**). CMR1 is also a member of the TRP family (so it is sometimes called *TRP8*), but it responds to *cool* temperatures and is found on small C fibers, so it transmits information about cool temperatures rather slowly (see Figure 8.22*a*). Another member of the TRP family is expressed by other free nerve endings to make them responsive to painfully cold temperatures, and this same receptor also responds to mustard oils (Jordt et al., 2004), which is why the wasabi we add to our sushi is so pungent.

THE PAIN RECEPTOR? The search for the protein receptor used by free nerve endings to detect *mechanical* damage was hindered by the fact that so many chemicals are released by damaged tissue. It was unclear which chemical was crucial for activating those particular nociceptors. But a family in northern Pakistan may have solved the question of the "pure" pain receptor protein for us. A 10-year-old boy there was giving street performances of piercing his arms with knives and walking on coals without pain. Before scientists could study him, he died after jumping off a roof to impress his friends.

This boy's apparent fearlessness, which cost him his life, reminds us that pain, and fear derived from pain, really can be our friend. Six of the boy's surviving relatives also felt no pain, although they could detect light touch, coolness, warmth, and other sensations. Scientists isolated the gene (called *SCN9A*) responsible for pain insensitivity in this family and found that it encodes a sodium channel expressed in many free nerve endings (Cox et al., 2006). There is great excitement that this sodium channel may represent the specific pain receptor protein, and that drugs targeted at this protein may provide new ways to relieve pain.


(a)
Channel activity
CMR1
TRPV1
TRP2
0
10
20
30
40
50
Temperature (°C)
CMR1 free nerve endings respond to low temperature.
TRPV1 free nerve endings respond to moderate heat.
TRP2 free nerve endings respond to high temperature.
(b)
Small, unmyelinated, slow C fibers carry signals from CMR1 and TRPV1 receptors, signaling cool temperature or dull pain, respectively.
Large, myelinated, fast Aδ fibers carry signals from TRP2 free nerve endings signaling sudden, sharp pain.
Skin
C fibers
Aδ fiber

8.22 Receptors That Detect Pain and Temperature (*a*) Free nerve endings with the cool-menthol receptor 1 (CMR1) are activated by temperatures below normal body temperature. Free nerve endings with the capsaicin receptor (TRPV1) respond to moderate heat and the capsaicin found in chili peppers. Other free nerve endings, with the related receptor protein TRP2, detect high temperatures. (*b*) The TRP2 free nerve endings transmit a fast action potential along large, myelinated Aδ fibers to the spinal cord. CMR1 and TRPV1 receptors transmit along slower, unmyelinated C fibers.

SPECIAL CNS PATHWAYS MEDIATE PAIN In the central nervous system, special pathways mediate pain and temperature information. Earlier we discussed the dorsal column system that carries touch information to the brain (see Figure 8.14). The sensation of pain and temperature is transmitted by the **anterolateral**, or **spinothalamic**, **system**. Free nerve endings in the skin send their axons to synapse on neurons in the dorsal horn of the spinal cord. These spinal cord neurons send their axons across the midline to the opposite side and up the anterolateral column of the spinal cord to the thalamus (hence the term *spinothalamic*). So, in the spinothalamic system pain information crosses the midline in the spinal cord before ascending to the brain (**Figure 8.23**); recall that touch information, in contrast, first ascends to the brainstem and then crosses the midline (see Figure 8.14). Either way, sensory information from one side of the body ends up in the opposite side of the brain.

The afferent fibers from the periphery that carry nociceptive information probably use **glutamate** as a neurotransmitter to excite spinal cells in the dorsal horn (S. Li and Tator, 2000), but they also release the neuromodulator **substance P**, which is a neuropep-

cool-menthol receptor 1 (CMR1) Also called *TRP8*. A sensory receptor found in some free nerve endings, that opens an ion channel in response to a mild temperature drop or exposure to menthol.

anterolateral system or spinothalamic system A somatosensory system that carries most of the pain information from the body to the brain.

glutamate An amino acid transmitter, the most common excitatory transmitter.

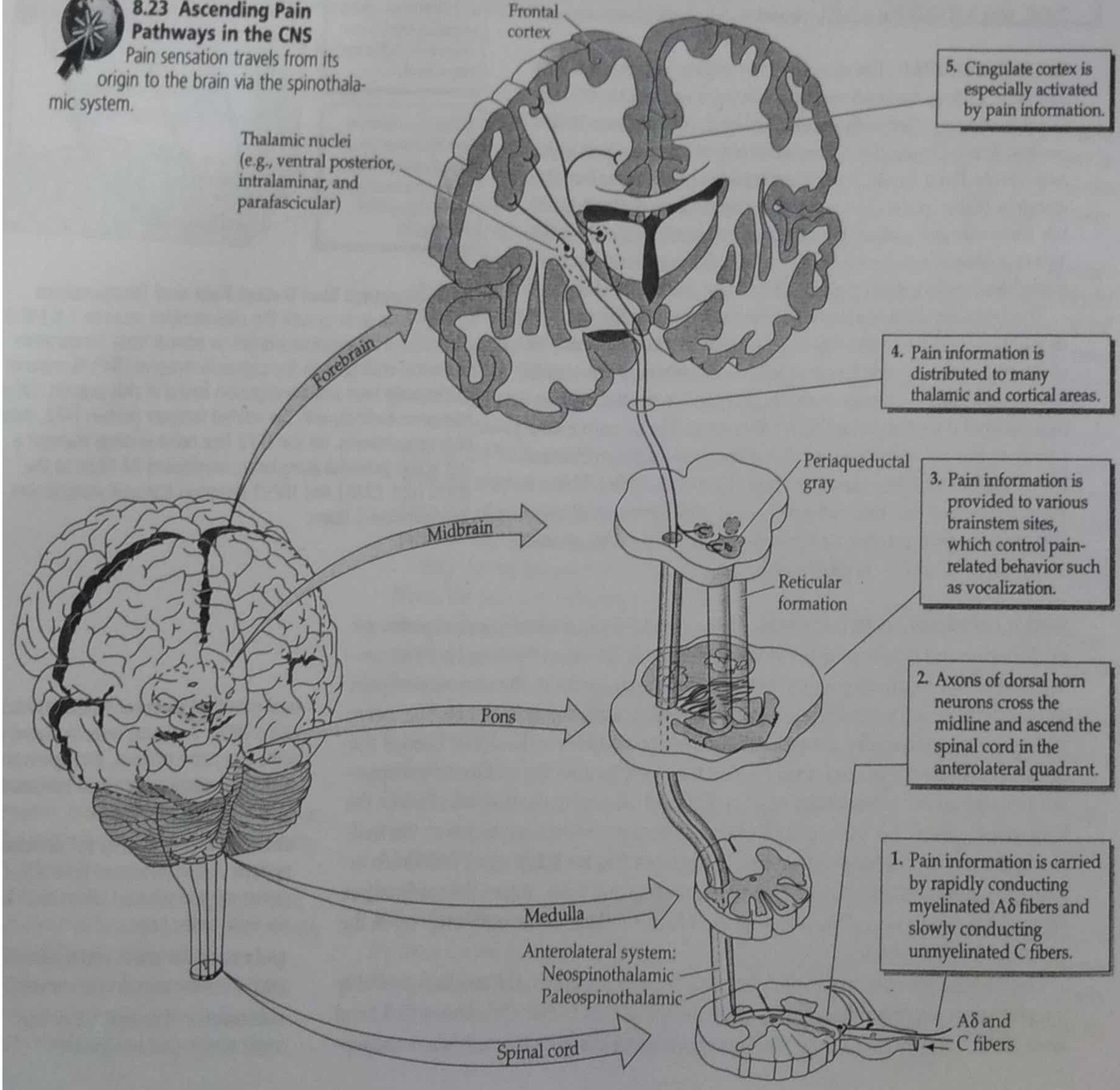
substance P A peptide transmitter implicated in pain transmission.

tide (the *P* stands for *peptide*). Injection of capsaicin into the skin provides a specific painful stimulus that leads to the release of substance P in the dorsal horn. There the postsynaptic neurons take up the substance P and begin remodeling their dendrites; investigators have speculated that this neural plasticity later affects pain perception, as we'll see shortly (Mantyh et al., 1997).

Further evidence that substance P plays a role in pain comes from experiments with knockout mice that lack either the gene for the precursor to substance P (Y. Cao et al., 1998) or a gene for the substance P receptor (De Felipe et al., 1998). (See Box 7.3 to review experimental techniques using knockout mice.) These mice are unresponsive to certain kinds of intense pain. Interestingly, they still respond to mildly painful stimuli, suggesting that other signals, perhaps the glutamate neurotransmitter, can carry that information. The dorsal horn neurons that receive this information, part of the spinothalamic system that we just described, send their axons across the midline and up the spinal cord to terminate in several nuclei of the thalamus (see Figure 8.23).

Sometimes pain persists long after the injury that gave rise to it has healed. The most dramatic example is a person's continued perception of chronic pain coming from a

8.23 Ascending Pain Pathways in the CNS Pain sensation travels from its origin to the brain via the spinothalamic system.


Frontal cortex
Thalamic nuclei (e.g., ventral posterior, intralaminar, and parafascicular)
Forebrain
Midbrain
Pons
Medulla
Spinal cord
Periaqueductal gray
Reticular formation
Anterolateral system:
Neospinothalamic
Paleospinothalamic
Aδ and C fibers

5. Cingulate cortex is especially activated by pain information.

4. Pain information is distributed to many thalamic and cortical areas.

3. Pain information is provided to various brainstem sites, which control pain-related behavior such as vocalization.

2. Axons of dorsal horn neurons cross the midline and ascend the spinal cord in the anterolateral quadrant.

1. Pain information is carried by rapidly conducting myelinated Aδ fibers and slowly conducting unmyelinated C fibers.

missing limb after loss of an arm or leg. Called *phantom limb pain*, this sensation is an example of **neuropathic pain**, so called because the pain seems to be due to inappropriate signaling of pain by neurons (rather than to tissue damage). Such cases can be seen as a disagreeable example of neural plasticity because the nervous system seems to have amplified its response to the pain signal (Woolf and Salter, 2000). Some of this amplification is taking place in the cortex (Flor et al., 2006), but changes in the spinal cord also contribute. After peripheral nerve injury (such as a damaged back or lost limb), microglial cells appear surrounding the synapses between pain fibers and neurons in the dorsal horn of the spinal cord (see Figure 8.23). These microglial cells release brain-derived neurotrophic factor (BDNF; see Chapter 7), which makes the dorsal horn neurons hyperexcitable: although GABA from other synapses had inhibited these neurons before, now GABA excites them. Thus the dorsal horn neurons become chronically active, flooding the thalamus with action potentials signaling pain.

Chronic pain can have dramatic effects on the brain. One study found evidence that the gray matter in dorsolateral prefrontal cortex of people with chronic back pain shrinks faster than in normal aging, averaging 1.3 mm^3 more per year of pain (Apkarian et al., 2004). This amount is estimated to be equivalent to 10 to 20 years of normal aging.

Cases of phantom limb pain are notoriously difficult to treat. In one type, the patient perceives that a missing limb is twisted and therefore hurts. Vilayanur Ramachandran has proposed a treatment for this condition: the patient looks at himself in a mirror, positioned in such a way that the reflection of the intact limb seems to have filled in for the missing limb. The patient then repeatedly moves "both limbs" (by moving the remaining one), watching closely the whole while, and sometimes reports that the phantom limb feels as though it has straightened out and no longer hurts (Ramachandran and Rogers-Ramachandran, 2000). This result suggests that the brain interprets the signals coming from the limb stump as painful, but visual stimuli may lead to a reinterpretation.

Pain information is eventually integrated in the **cingulate cortex**. Recall from Chapter 1 that the cingulate cortex is much more activated by a stimulus if people are led to believe that the stimulus will be painful (see Figure 1.4) (Rainville et al., 1997). The extent of activation in the cingulate (as well as the somatosensory cortex) also correlates with how much discomfort different people report in response to the same mildly painful stimulus (Coghill et al., 2003). Studies suggest that the emotional and sensory components of pain are associated with different subregions of the cingulate cortex (Vogt, 2005). In people *experiencing* pain, both rostral and caudal cingulate were activated; but when they were *empathizing* with a loved one who was experiencing pain, only the rostral cingulate was activated (T. Singer et al., 2004).

The cingulate cortex is also activated in people experiencing illusory pain (Craig et al., 1996): placing your hand over alternating pipes of cool and warm (not hot) water produces the sensation of pain, as though the pipes were hot. Presumably this illusory pain sensation is produced by the unusual circumstance of neighboring CMR1 and TRPV1 receptors being stimulated at the same time. Because no tissue is actually being damaged, this is a wonderful illustration that "pain is in the brain."

Pain can be controlled by a variety of mechanisms and pathways

Relief from the suffering of pain has long been a dominant concern of humans. Throughout history, different remedies have been offered. One frustrating, puzzling aspect of pain pathways is that cutting the pathway reduces pain perception only temporarily. After a pathway in the spinal cord is cut, pain is initially diminished, but it returns in a few weeks or months.

The usual way that these data are interpreted is that nociceptive input from the remaining intact pathways becomes abnormally effective. In an enormously influential paper, Melzack and Wall (1965) suggested that pain is subject to many modulating influences, including some that can close spinal "gates" controlling the flow of pain information from the spinal cord to the brain. Maybe the spinal gates get stuck open in some people, sending pain signals continuously, and maybe we could find strategies to

neuropathic pain Pain caused by damage to peripheral nerves; often difficult to treat.

cingulate cortex Also called *cingulum*. A region of medial cerebral cortex that lies dorsal to the corpus callosum.

close those gates to alleviate pain. In the sections that follow, we will discuss some of these strategies, which are prime examples of the interaction between basic research and application.

OPIATE DRUGS Opium has been used for **analgesia** (loss of pain sensation; from the Greek *an-*, "not," and *algesis*, "feeling of pain") for centuries. Modern researchers attempting to determine how **opiates** (drugs, such as morphine, that are derived from or related to opium) control pain finally showed that the brain contains natural opiate-like substances, or **opioids**. In effect, the brain modulates pain in a manner akin to how exogenous opiates such as morphine do. Three classes of endogenous opiates—**endorphins**, **enkephalins**, and **dynorphins**—have been discovered (see Chapter 4), and several classes of **opioid receptors** have been identified and designated by Greek letters. Of these, the mu (μ) receptor seems to be most affected by morphine. There are interesting individual differences in opioid receptor function. For example, analgesics that act on μ receptors are more effective in men than in women, and drugs that act on the kappa (κ) receptor are more effective in women than in men (Mogil and Chanda, 2005). Furthermore, the κ receptor–specific drugs are especially effective in redheaded women (Mogil et al., 2003).

Early observations showed that electrical stimulation of the **periaqueductal gray** area (see Figure 8.23) of the brainstem in rats produces potent analgesia. Injection of opiates into this area also relieves pain, suggesting that the region contains synaptic receptors for opiate-like substances. The periaqueductal gray area receives strong input from the spinal cord, which presumably delivers nociceptive information.

According to one model, the brainstem controls pain transmission in the spinal cord (Basbaum and Fields, 1978, 1984). Periaqueductal gray neurons send endorphin-containing axons to stimulate neurons in the medulla. These medullary neurons send serotonin-containing axons to the spinal cord to inhibit the neurons that transmit information from the periphery. In this way, pain information is blocked by a direct gating action in the spinal cord. Electrical stimulation of the descending tract elicits inhibition of the response of spinal cord sensory relay cells to noxious stimulation of the skin. **Figure 8.24** shows both the ascending pain communication system and the descending pain control system.

In addition to their beneficial pain-relieving effects, opiates and other analgesics (painkillers) often produce side effects such as confusion, drowsiness, vomiting, constipation, and depression of the respiratory system. Now that we know the circuitry of the pain relief system, why give large doses of the drug systemically (i.e., throughout the body)? Instead, physicians can administer very small doses of opiates directly to the spinal cord to relieve pain, thus avoiding many of the side effects. The drugs can be administered *epidurally* (just outside the spinal cord's dura mater) or *intrathecally* (between the dura mater and the spinal cord). Both routes are somewhat invasive and therefore are restricted to surgical anesthesia, childbirth, or the management of severe chronic pain (Landau and Levy, 1993).

There have been long-standing concerns about the use of morphine and other opiates for pain relief because of their addictive potential. Low doses and infrequent use were the common standard. However, the Agency for Healthcare Research and Quality urges swift use of painkillers after surgery. Once chronic pain develops, it is extremely difficult to overcome, so the best approach is to prevent the onset of chronic pain by early, aggressive treatment. The danger of addiction from the use of morphine to relieve surgical pain has been vastly overexaggerated (Melzack, 1990); it is no more than 0.04% (Brownlee and Schrof, 1997). In the media, people addicted to painkillers are often said to have "gotten hooked" when given a prescription for pain. But further investigations reveal that almost all of these people had been drug abusers *before* they were given a prescription for pain (Szalavitz, 2004). Unfortunately, the myth that opiate treatment leads to addiction results in millions of people being undertreated for pain each year (Quill and Meier, 2006).

Other, nonopioid analgesics may be available soon. For example, a toxin from a marine snail (Sandall et al., 2003) is a very potent analgesic recently approved by the FDA

analgesia Absence of or reduction in pain.

opiates A class of compounds that exert an effect like that of opium, including reduced pain sensitivity.

opioids A class of peptides produced in various regions of the brain that bind to opiate receptors and act like opiates.

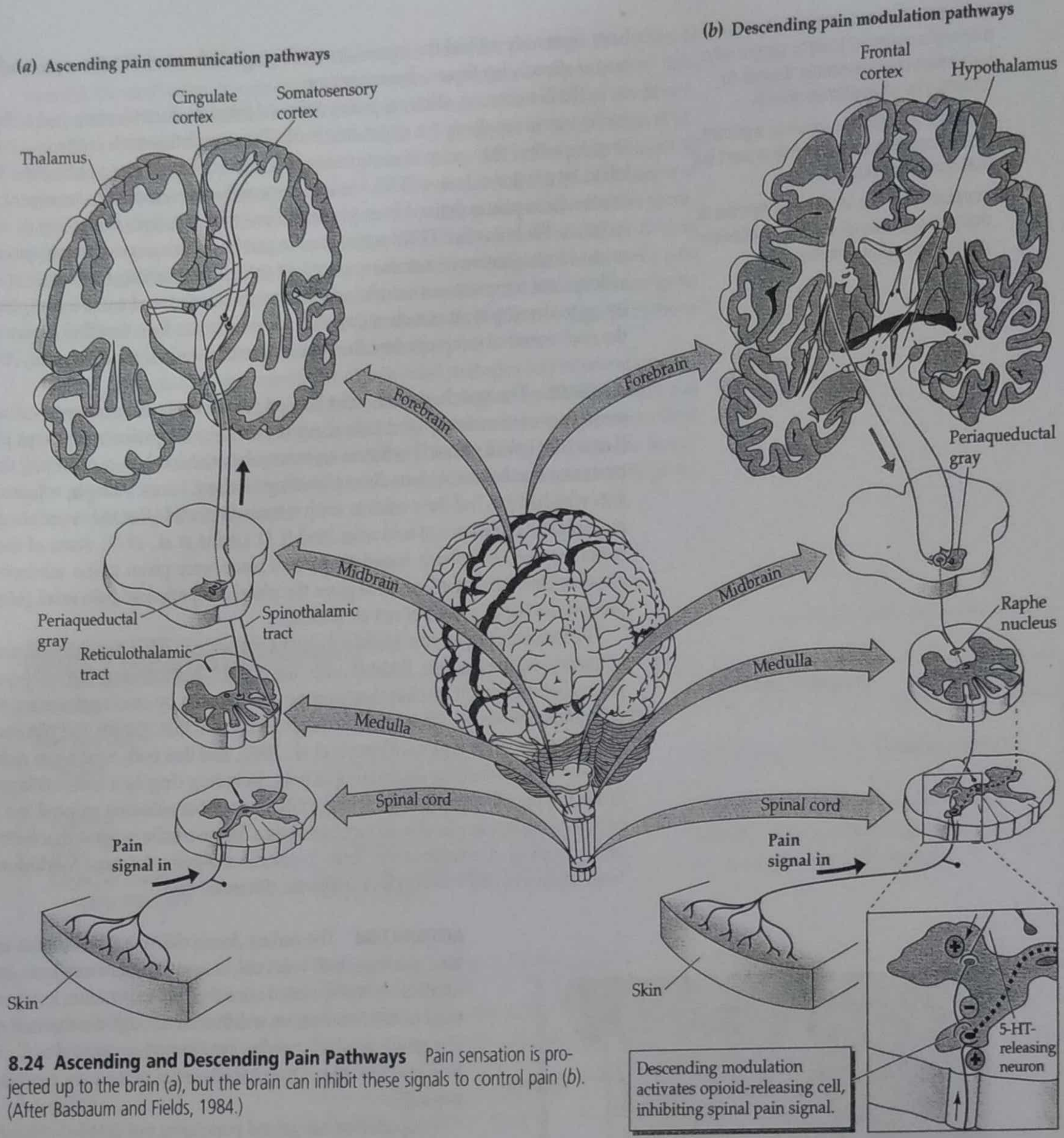
endorphins One of three kinds of endogenous opiates.

enkephalins One of three kinds of endogenous opiates.

dynorphins One of three kinds of endogenous opiates.

opioid receptor A receptor that responds to endogenous and/or exogenous opiates.

periaqueductal gray The neuronal body–rich region of the midbrain surrounding the cerebral aqueduct, involved in pain perception.


(a) Ascending pain communication pathways
Cingulate cortex
Somatosensory cortex
Thalamus
Periaqueductal gray
Spinothalamic tract
Reticulothalamic tract
Pain signal in
Skin
Forebrain
Midbrain
Medulla
Spinal cord
(b) Descending pain modulation pathways
Frontal cortex
Hypothalamus
Periaqueductal gray
Raphe nucleus
Pain signal in
Skin
5-HT-releasing neuron
+
−
+

8.24 Ascending and Descending Pain Pathways Pain sensation is projected up to the brain (*a*), but the brain can inhibit these signals to control pain (*b*). (After Basbaum and Fields, 1984.)

Descending modulation activates opioid-releasing cell, inhibiting spinal pain signal.

as PRIALT. Unfortunately, the drug has severe side effects unless delivered directly to the spinal cord, so its use is limited. The recent evidence that nerve growth factor (NGF; see Chapter 7) is one of the factors released by mechanical damage to trigger nociceptors is prompting the search for NGF receptor blockers that might alleviate pain (Summer et al., 2006).

STIMULATION OF THE SKIN Humans have tried a lot of strange techniques to relieve pain. Centuries ago, for example, electric fishes or eels were applied to sites of pain. A modern version of such treatment, called **transcutaneous electrical nerve stimulation (TENS)**, can suppress certain types of pain that are difficult to control. For some reason, stimulating the nerves around the source of pain provides relief, perhaps by closing the spinal "gate" for pain that Melzack and Wall (1965) spoke of. Recall, for example, the last time you stubbed your toe. In addition to expelling a string of expletives, you may

transcutaneous electrical nerve stimulation (TENS) The delivery of electrical pulses through electrodes attached to the skin, which excite nerves that supply the region to which pain is referred. TENS can relieve the pain in some instances.

naloxone A potent antagonist of opiates that is often administered to people who have taken drug overdoses. It binds to receptors for endogenous opioids.

placebo A substance, given to a patient, that is known to be ineffective or inert but that sometimes brings relief.

acupuncture The insertion of needles at designated points on the skin to alleviate pain or neurological malfunction.

have vigorously rubbed the injured area, bringing a little relief. TENS is a more efficient way of stimulating those adjacent nerves.

In TENS treatment, electrical pulses delivered through electrodes attached to the skin excite nerves supplying the region that hurts. The stimulation itself produces a sense of tingling rather than pain. In some cases dramatic relief of pain can outlast the stimulation by a factor of hours. TENS has been especially successful in the treatment of patients whose pain is derived from peripheral nerve injuries such as arthritis or surgical incisions. We know that TENS acts at least in part by releasing endogenous opioids, because administration of **naloxone**, an opioid antagonist, partially blocks this analgesic action. Cool temperatures can also soothe peripheral pain, and some investigators are trying to develop synthetic chemicals that are even better than menthol at stimulating the cool-menthol receptors described earlier to relieve pain (Proudfoot et al., 2006).

PLACEBOS The search for pain relief has led people to consume many unusual substances; even chemically inert pills alleviate pain in many patients. The term **placebo** (Latin for "I shall please") refers to an inert substance (such as a sugar pill) or other treatment that has no obvious direct physiological effect. In one example, volunteer subjects who had just had their wisdom teeth extracted were told that they were being given an analgesic but were not told what kind (J. D. Levine et al., 1978). Some of these patients received morphine-based drugs, and some were given saline solutions—the placebo. One out of three patients given the placebo experienced pain relief. (Morphine produced relief in most, but not all, patients.)

The researchers gave the opioid antagonist naloxone to other patients who were also administered the placebo. Patients given the placebo *and* naloxone did not experience pain relief; this result implies that placebo relieves pain by causing the release of endogenous opioids. Functional brain imaging indicates that opioids and placebos activate the same brain regions (Petrovic et al., 2002), and that both treatments reduce the activity of brain regions responding to pain, including cingulate cortex (Wager et al., 2004). On the other hand, Grevert et al. (1983) found that naloxone reduced, but did not completely prevent placebo-induced analgesia. These results suggest that both opioid and nonopioid mechanisms contribute to placebo analgesia; the same conclusion comes from studies of other methods of analgesia, discussed next.

ACUPUNCTURE The earliest description of pain relief from **acupuncture** is at least 3000 years old. In some acupuncture procedures the needles are manipulated once they are in position; in others, electrical or heat stimulation is delivered through the inserted needles. The points at which needles are inserted are related to the locus of pain and to some of the characteristics of the pain condition (**Figure 8.25**).

Acupuncture has gained popularity, but detailed clinical assessments indicate that only some people achieve continued relief from chronic pain. At least part of the pain-blocking character of acupuncture appears to be mediated by the release of endorphins (N. M. Tang et al., 1997). Administering opioid antagonists such as naloxone prior to acupuncture blocks or reduces its pain control effects. More research is needed in clinical settings to identify the limits of this type of pain control.

8.25 Acupuncture for Controlling Pain In some cases, acupuncture for controlling pain induces the release of endogenous opiates, because opioid antagonists may interfere with the analgesia.

STRESS A deer fleeing an encounter with a mountain lion would do well to ignore any pain from injuries for the moment. Similarly, sometimes people badly hurt in traumatic circumstances report little or no immediate pain. Laboratory studies demonstrate the existence of pain control circuitry, but they don't tell us how the inhibitory systems are normally activated.

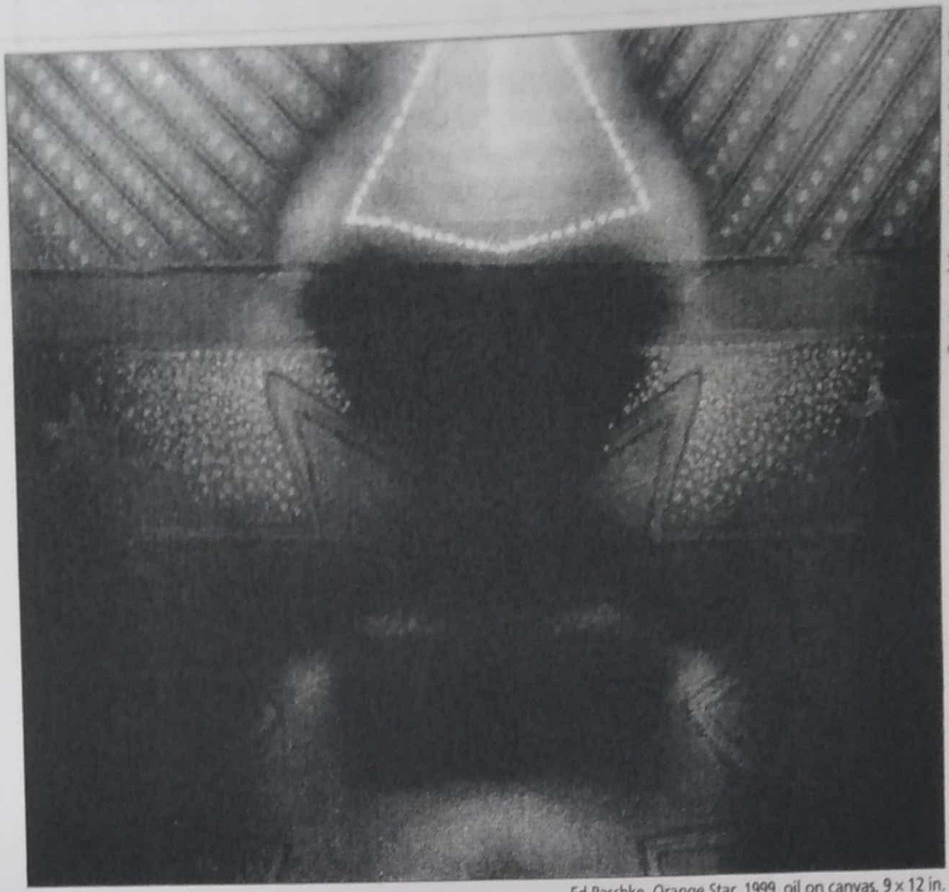
To answer this question, researchers have examined pain inhibition that arises in stressful circumstances. It appears that brain systems produce analgesia when pain threatens to overwhelm effective coping strategies. For example, exposing rats to several different kinds of inescapable foot shock induces analgesia in rats (Terman et al., 1984). When analgesia is produced by *short* periods of foot shock, the opiate antagonist naltrexone reverses the analgesic response—a result demonstrating that the source of analgesia is an opioid system in the brain. However, naltrexone has little effect on stress-induced analgesia if the duration or intensity of foot shock is altered. This finding demonstrates that stress activates both an opioid-sensitive analgesic system and a pain control system that does *not* involve opioids. In some cases, the nonopioid analgesia is caused by the release of cannabinoids (Hohmann et al., 2005), endogenous versions of the active ingredient in marijuana (see Chapter 4).

Table 8.3 summarizes the many types of pain relief strategies and interventions, including surgical and pharmacological strategies, psychological treatments, brain and spinal cord stimulation, and sensory stimulation. The elusive nature of pain is evident in this range of potential interventions, some of which reflect desperation in the face of great anguish. As we learn more about how the brain controls pain, we can hope for better, safer analgesics in the future.

TABLE 8.3 Types of Pain Relief Intervention

Measure	Mechanism	Limitations/comments
PSYCHOGENIC		
Placebo	May activate endorphin-mediated pain control system	Sometimes inhibited by opiate antagonists
Hypnosis	Alters brain's perception of pain	Control unaffected by opiate antagonists
Stress	Both opioid and nonopioid mechanisms	Clinically impractical and inappropriate
Cognitive (learning, coping strategies)	May activate endorphin-mediated pain control system	Limited usefulness for severe pain
PHARMACOLOGICAL		
Opiates	Bind to opioid receptors in periaqueductal gray and spinal cord	Severe side effects due to binding in other brain regions
Spinal block	Drugs block pain signals in spinal cord	Avoids side effects of systemic administration
Anti-inflammatory drugs	Block prostaglandin and leukotriene synthesis at site of injury	Major side effects
Aspirin	Blocks prostaglandin synthesis (see Figure 8.21) at site of injury	Does not block leukotriene synthesis
STIMULATION		
TENS/mechanical	Tactile or electrical stimulation of large fibers blocks or alters pain signal to brain	Segmental control; must be applied at site of pain
Acupuncture	Seems similar to TENS	Sometimes affected by opiate antagonists
Central gray	Electrical stimulation activates endorphin-mediated pain control systems, blocking pain signal in spinal cord	Control inhibited by opiate antagonists
SURGICAL		
Cut peripheral nerve cord Rhizotomy (cutting dorsal root) Cord hemisection	Create physical break in pain pathway	Considerable risk of failure or return of pain
Frontal lobotomy	Disrupts affective response to pain	Irreversible; risky; severe effects on behavior

CHAPTER 9



Courtesy of the artist and Maya Polsky Gallery

Ed Paschke, *Orange Star*, 1999, oil on canvas, 9 × 12 in.

CONTENTS

Hearing 249

Each Part of the Ear Performs a Specific Function in Hearing 250

Auditory System Pathways Run from the Brainstem to the Cortex 256

Two Main Theories Describe How We Discriminate Pitch 258

By Comparing the Ears, We Can Localize Sounds 260

The Auditory Cortex Performs Complex Tasks in the Perception of Sound 262

Deafness Is a Major Disorder of the Nervous System 265

Vestibular Perception 267

The Receptor Mechanisms for the Vestibular System Are in the Inner Ear 268

Evolution Has Shaped the Auditory and Vestibular End Organs 269

Nerve Fibers from the Vestibular Portion of the Vestibulocochlear Nerve (VIII) Synapse in the Brainstem 269

Some Forms of Vestibular Excitation Produce Motion Sickness 270

The Chemical Senses: Taste and Smell 270

Chemicals in Tastants Elicit Taste Sensations 271

Chemicals in the Air Elicit Odor Sensations 274

Hearing, Vestibular Perception, Taste, and Smell

No Ear for Music

Given the category "wedding music," you will probably immediately think of a tune or two that you can hear in your head—perhaps "The Wedding March" or, less fortunately, "The Chicken Dance." The same goes for Beethoven's Fifth Symphony, or the theme from *Star Wars*. These pieces of music, and others like them, are tunes that most people can identify right away, after hearing just a few bars. But Tony is different.

Tony is completely flummoxed by music. His ability to understand pitch, and the relationships between chords, is nearly at chance levels. Although he is happy to try to belt out a song, he is unable to sing in tune and doesn't even recognize that he is singing off-key unless he is told so by a (grimacing) friend. He cannot identify the tune to "Happy Birthday" unless he also hears the lyrics, in which case he can identify it immediately. Yet he has no problem with nonmusical uses of pitch, such as the rising tone at the end of a question.

Tony is a man of better-than-average intelligence, with perfectly normal cognitive functioning, except for his lifelong inability to appreciate music despite years of childhood music lessons. This highly specific difficulty with music is an affliction that Tony has in common with many other people; revolutionary Che Guevara and Nobel Prize–winning economist Milton Friedman are two noted examples.

What is the nature of this mysterious problem? Is it a kind of hearing problem? A learning disability?

You exist only because your ancestors had keen senses that allowed them to find food and to avoid predators and other dangers. In this chapter we turn to systems that allow us to sense signals from distant sources, particularly sounds (audition) and smells (olfaction). We also discuss related systems for detecting position and movement of the body (the vestibular system, related to the auditory system) and tastes of foods (the gustatory or taste sense, which, like olfaction, is a chemical sense). We begin with hearing because audition evolved from special mechanical receptors related to the somatosensory elements that we discussed in Chapter 8.

Hearing

Hearing is an important part of the adaptive behavior of many animals. For humans, the sounds of speech form the basic elements of languages and therefore of social relations. Helen Keller, who was both blind and deaf, said, "Blindness deprives you of contact with things; deafness deprives you of contact with people."

The sounds of any single language are only a small subset of the enormous variety of sounds that can be produced by the human vocal cavity. The sounds produced by animals—from insects to whales—also have a wide range of complexity, in keeping with their adaptive significance. For example, the melodic songs of male birds and the chirps of male crickets attract females of their species. The grunts, screeches, and burbly sounds of primates signal danger or the need for comfort or satisfaction. Elephants can recognize individuals by their calls (McComb et al., 2000). Owls and bats exploit the directional property of sound to locate prey and avoid obstacles in the dark, and whales employ sounds that can travel hundreds of miles in the ocean. Unlike visual stimuli, sounds can go around obstacles, and they work as well in the dark as in the light.

transduction The conversion of one form of energy to another.

external ear The part of the ear that we readily see (the pinna) and the canal that leads to the eardrum.

pinna The external part of the ear.

Your auditory system detects rapid changes of sound intensity (measured in decibels, dB) and frequency (measured in hertz, Hz). In fact, the speed of auditory information processing is so good that the analysis of frequency by the human ear rivals that of modern electronic gadgets. Your ear is so sensitive to sounds in the middle of the hearing range that, if it were any more sensitive, you would be distracted by the noise of air molecules bouncing against each other in your ear canal! **Box 9.1** describes some basic properties of sound.

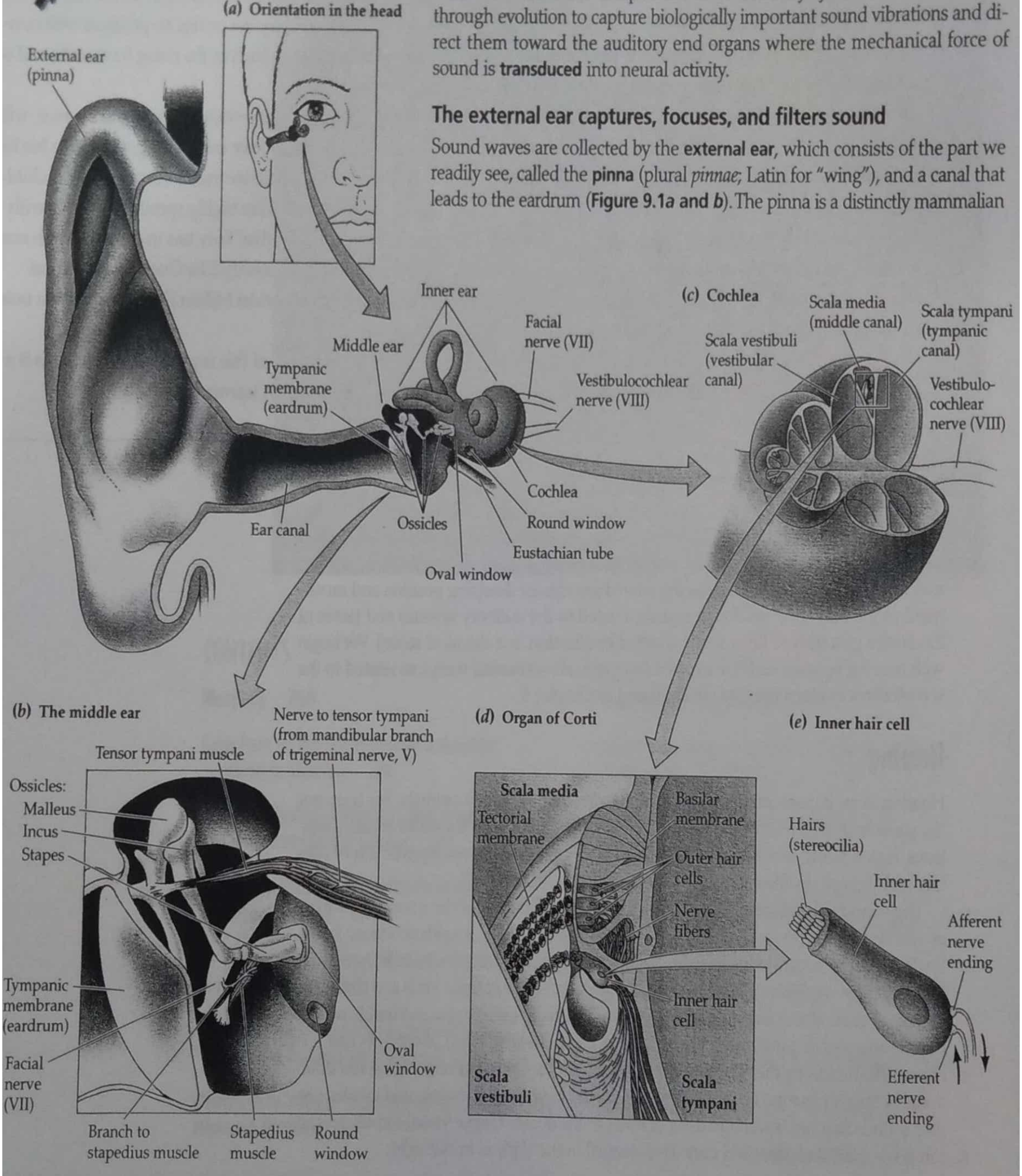
Each Part of the Ear Performs a Specific Function in Hearing

How do small vibrations of air molecules become the speech, music, and other sounds we hear? The components of the auditory system have been shaped through evolution to capture biologically important sound vibrations and direct them toward the auditory end organs where the mechanical force of sound is **transduced** into neural activity.

The external ear captures, focuses, and filters sound

Sound waves are collected by the **external ear**, which consists of the part we readily see, called the **pinna** (plural *pinnae*; Latin for "wing"), and a canal that leads to the eardrum (**Figure 9.1*a* and *b***). The pinna is a distinctly mammalian

9.1 External and Internal Structures of the Human Ear


(a) Orientation in the head
External ear (pinna)
Inner ear
Middle ear
Tympanic membrane (eardrum)
Facial nerve (VII)
Vestibulocochlear nerve (VIII)
Cochlea
Round window
Eustachian tube
Oval window
Ossicles
Ear canal
(c) Cochlea
Scala media (middle canal)
Scala tympani (tympanic canal)
Scala vestibuli (vestibular canal)
Vestibulocochlear nerve (VIII)
(b) The middle ear
Nerve to tensor tympani (from mandibular branch of trigeminal nerve, V)
Tensor tympani muscle
Ossicles:
Malleus
Incus
Stapes
Tympanic membrane (eardrum)
Facial nerve (VII)
Oval window
Branch to stapedius muscle
Stapedius muscle
Round window
(d) Organ of Corti
Scala media
Tectorial membrane
Basilar membrane
Outer hair cells
Nerve fibers
Inner hair cell
Scala vestibuli
Scala tympani
(e) Inner hair cell
Hairs (stereocilia)
Inner hair cell
Afferent nerve ending
Efferent nerve ending

characteristic, and mammals show a wide array of ear shapes and sizes. The acoustic properties of the external ear are important because its shape physically transforms sound energies.

The "hills and valleys" of the pinna modify the character of sound that reaches the middle and inner ear. Some frequencies of sound are enhanced; others are suppressed. For example, the shape of the human ear especially increases the reception of sounds between 2000 and 5000 Hz, a frequency range that is important for speech perception. The shape of the external ear is also important in sound localization—that is, identifying the direction and distance of the source of a sound (discussed later in this chapter).

Although (some) humans can move their ears only enough to entertain children, many other mammals deftly shape and swivel their pinnae to help determine the source of a sound. Animals with exceptional auditory localization abilities, such as bats, may have especially mobile ears. Of course, animals with mobile ears have to take into account the position of the pinna when interpreting sounds around them. Information about the position of the external ear in such animals is conveyed to the auditory pathways in several forms, including feedback information from receptors in the muscles around the pinna.

The middle ear concentrates sound energies

Between the external ear and the receptor cells of the inner ear is a group of structures, including bones and muscles, that constitute the **middle ear** (see Figure 9.1*b*). A chain of three tiny bones, or **ossicles**, connects the **tympanic membrane** (eardrum) at the end of the ear canal to an opening of the inner ear called the **oval window**. These ossicles, the smallest bones in the body, are called the **malleus** (Latin for "hammer"), the **incus** (Latin for "anvil"), and the **stapes** (Latin for "stirrup").

Small displacements of the tympanic membrane move the chain of ossicles. These bones help concentrate the tiny mechanical forces of vibrating air particles, focusing the pressures from the relatively large tympanic membrane onto the small oval window. This arrangement vastly amplifies sound pressure so that it can produce movement in the fluid of the inner ear.

The mechanical linkage of the ossicles is not fixed; two muscles vary the linkage to improve auditory perception and protect the delicate inner ear from loud, potentially damaging sounds. One of these muscles, the **tensor tympani** (see Figure 9.1*b*), is attached to the malleus, which is connected to the tympanic membrane. The other muscle of the middle ear is attached to the stapes and thus is called the **stapedius**. When activated, these muscles stiffen the linkages of the middle-ear bones, thus reducing the effectiveness of sounds.

The muscles of the middle ear are activated by sounds that are 80 to 90 dB above a person's hearing threshold—about as loud as a noisy street. When a loud sound reaches the ear, the stapedius muscle starts to contract about 200 ms later. The middle-ear muscles also attenuate self-made sounds; without this system, body movement, swallowing, vocalizations, and other internally produced sounds would be distractingly loud. Species that produce especially loud calls, such as bats, rely on this system to protect their auditory receptors from physical damage (Avan et al., 1992). Interestingly, the middle-ear muscles contract just *before* the self-made sound occurs, demonstrating that the system is controlled in a complex manner. People whose middle-ear muscles have been damaged by disease complain about the annoying loudness of sounds that they formerly ignored.

The cochlea converts vibrational energy into waves of fluid

The complex structures of the **inner ear** (Figure 9.1*c*) ultimately convert sound into neural activity. In mammals the auditory portion of the inner ear is a coiled, fluid-filled structure called the **cochlea** (from the Greek *kochlos*, "snail") (**Figure 9.1c and *d***). Embedded in the temporal bone of the skull, the human cochlea is a marvel of miniaturization. In an adult, the cochlea measures only about 4 mm in diameter—about the size of a pea. Unrolled, the cochlea would measure about 35 to 40 mm in length.

middle ear The cavity between the tympanic membrane and the cochlea.

ossicles Three small bones (incus, malleus, and stapes) that transmit sound across the middle ear, from the tympanic membrane to the oval window.

tympanic membrane Also called *eardrum*. The partition between the external ear and the middle ear.

oval window The opening from the middle ear to the inner ear.

malleus Latin for *hammer*. A middle-ear bone that is connected to the tympanic membrane.

incus Latin for *anvil*. A middle-ear bone situated between the malleus and the stapes.

stapes Latin for *stirrup*. A middle-ear bone that is connected to the oval window.

tensor tympani The muscle attached to the malleus and the tympanic membrane that modulates mechanical linkage to protect the delicate receptor cells of the inner ear from damaging sounds.

stapedius A middle-ear muscle that is attached to the stapes.

inner ear The cochlea and vestibular apparatus.

cochlea A snail-shaped structure in the inner ear that contains the primary receptor cells for hearing.

BOX 9.1 The Basics of Sound

We perceive a repetitive pattern of local increases and decreases in air pressure as sound. Usually this oscillation is caused by a vibrating object, such as a tuning fork or a person's larynx while speaking. A single alternation of compression and expansion of air is called one *cycle*.

Figure A illustrates the changes in pressure produced by a vibrating tuning fork. Because the sound produced by a tuning fork has only one frequency of vibration, it is called a **pure tone** and can be represented by a sine wave. A pure tone is described physically in terms of two measures:

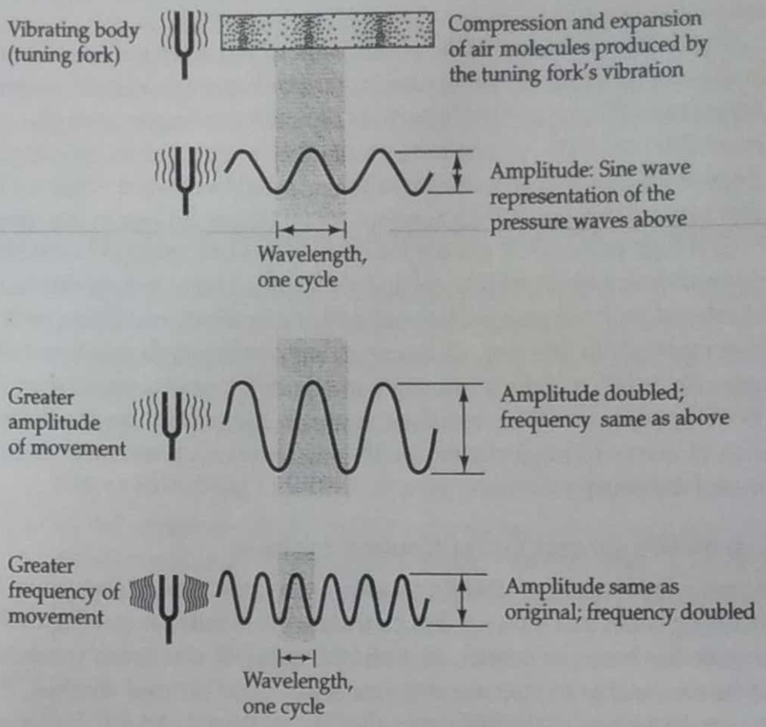
1. **Frequency**, or the number of cycles per second, measured in **hertz (Hz)**. For example, middle A on a piano has a frequency of 440 Hz. Our perception of frequency is termed **pitch**.
2. **Amplitude**, or intensity—usually measured as sound pressure, or force per unit area, in dynes per square centimeter (dyn/cm^2). Our perception of amplitude is termed **loudness**.

Most sounds are more complicated than a pure tone. For example, a sound made by a musical instrument contains a fundamental frequency and harmonics. The **fundamental** is the basic frequency, and the **harmonics** are multiples of the fundamental. Thus, if the fundamental is 440 Hz, the harmonics are 880, 1320, 1760, and so on. When different instruments play the same note, the notes differ in the relative intensities of the various harmonics; this difference is what gives each instrument its characteristic sound quality, or **timbre**.

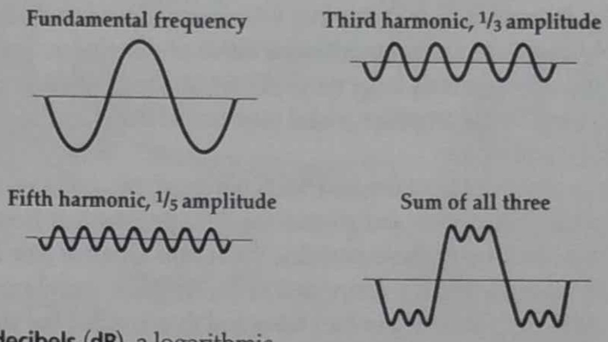
Any complex sound can be decomposed into a sum of simple sine waves, through a mathematical process called **Fourier analysis**. (We will see in Chapter 10 that Fourier analysis can also be applied to visual patterns.) Figure B shows how several pure-tone sine waves can be summed to produce a complex waveform.

Because the ear is sensitive to a huge range of sound pressures, sound intensity (a measure of the difference between two pressures) is usually expressed in **decibels (dB)**, a logarithmic scale. The common reference level for human hearing is 0.0002 dyn/cm^2, the smallest amplitude at which an average human ear can detect a 1000-Hz tone. A faint whisper is about ten times as intense, and a jet airliner 500 feet overhead is about a million times as intense. The whisper is about 20 dB above threshold, and the jetliner is about 120 dB above threshold. Normal conversation is about 60 dB above the reference level.

(A) Amplitude and frequency of sound waves


Vibrating body (tuning fork)
Compression and expansion of air molecules produced by the tuning fork's vibration
Amplitude: Sine wave representation of the pressure waves above
Wavelength, one cycle
Greater amplitude of movement
Amplitude doubled; frequency same as above
Greater frequency of movement
Amplitude same as original; frequency doubled
Wavelength, one cycle

(B) Fourier analysis


Fundamental frequency
Third harmonic, 1/3 amplitude
Fifth harmonic, 1/5 amplitude
Sum of all three

pure tone A tone with a single frequency of vibration.

frequency The number of cycles per second in a sound wave; measured in hertz (Hz).

hertz (Hz) Cycles per second, as of an auditory stimulus.

pitch A dimension of auditory experience in which sounds vary from low to high.

amplitude The distance of particle movement in a defined period of time, usually measured as dynes per square centimeter.

loudness The subjective experience of the pressure level of a sound.

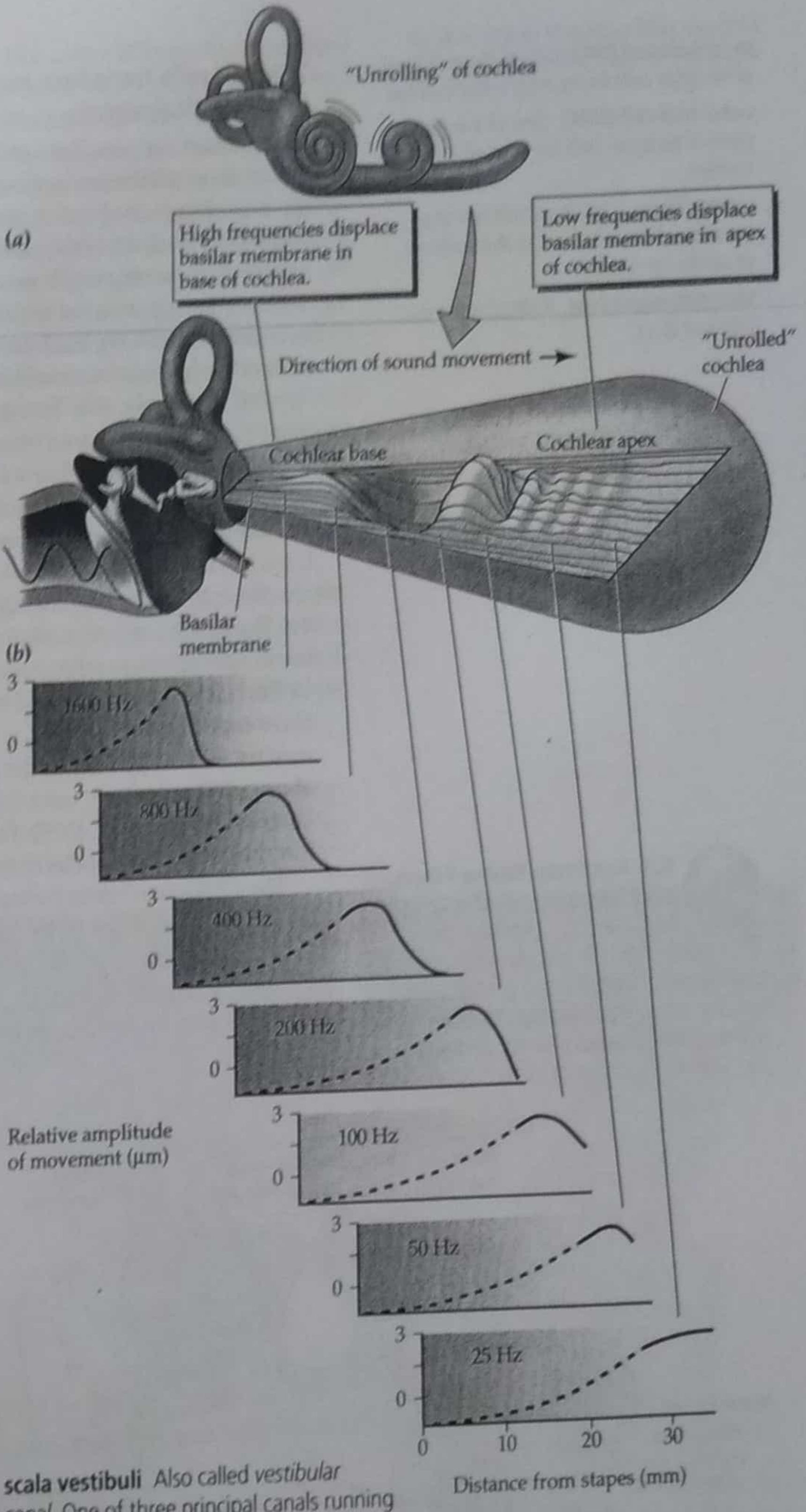
fundamental The predominant frequency of an auditory tone or a visual scene.

harmonics Multiples of a particular frequency called the *fundamental*.

timbre The characteristic sound quality of a musical instrument, as determined by the relative intensities of its various harmonics.

Fourier analysis The analysis of a complex pattern into the sum of sine waves.

decibel (dB) A measure of sound intensity.


"Unrolling" of cochlea
(a)
High frequencies displace basilar membrane in base of cochlea.
Low frequencies displace basilar membrane in apex of cochlea.
Direction of sound movement →
"Unrolled" cochlea
Cochlear base
Cochlear apex
Basilar membrane
(b)
1600 Hz
800 Hz
400 Hz
200 Hz
100 Hz
50 Hz
25 Hz
3
0
Relative amplitude of movement (μm)
0
10
20
30
Distance from stapes (mm)

9.2 Basilar Membrane Movement for Sounds of Different Frequencies In this illustration the basilar membrane is represented as uncoiled. (*a*) Displacement of the basilar membrane peaks at the cochlear base for high frequencies and at the apex for low frequencies. (*b*) As the frequency (measured in hertz [Hz], or cycles per second) of stimulation decreases, the position of the peak of membrane movement is displaced progressively toward the apex of the cochlea.

The region nearest the oval-window membrane is the *base* of the spiral; the other end is referred to as the *apex*. The cochlea is a coil of three parallel canals: (1) the **scala vestibuli** (*vestibular canal*), (2) the **scala media** (*middle canal*), and (3) the **scala tympani** (*tympanic canal*) (see Figure 9.1*c*). Because the entire structure is filled with noncompressible fluid, movement within the cochlea in response to a push on the oval window requires the presence of a movable outlet membrane. This membrane is the **round window**, which separates the scala tympani from the middle ear (see Figure 9.1*b*).

The principal components that do the work of converting sounds into neural activity, collectively known as the **organ of Corti** (see Figure 9.1*d*), consist of three main structures: (1) the sensory cells (**hair cells**), (2) an elaborate framework of supporting cells, and (3) the terminations of the auditory fibers. The base of the organ of Corti is the **basilar membrane**. This flexible membrane separates the scala tympani from the scala media, and importantly, it vibrates in response to sound. The basilar membrane is about five times wider at the apex of the cochlea than at the base, even though the cochlea itself narrows toward its apex.

When the stapes moves in and out as a result of acoustic vibrations, it exerts varying pressure on the fluid of the scala vestibuli, which in turn causes oscillating movements of the basilar membrane. Georg von Békésy (1890–1972) demonstrated that different parts of the basilar membrane are affected by different frequencies of sound. The site of the largest amplitude of displacement of the basilar membrane depends on the frequency of the stimulus (**Figure 9.2**). High frequencies cause maximal displacement of the basilar membrane near the base, where the membrane is narrow. For low-frequency stimuli, displacement of the basilar membrane is greatest in regions where the membrane is wider—toward the apex (Ashmore, 1994).

scala vestibuli Also called *vestibular canal*. One of three principal canals running along the length of the cochlea.

scala media Also called *middle canal*. The central of the three spiraling canals inside the cochlea, situated between the scala vestibuli and the scala tympani.

scala tympani Also called *tympanic canal*. One of three principal canals running along the length of the cochlea.

round window A membrane separating the cochlear duct from the middle-ear cavity.

organ of Corti A structure in the inner ear that lies on the basilar membrane of the cochlea and contains the hair cells and terminations of the auditory nerve.

hair cell One of the receptor cells for hearing in the cochlea.

basilar membrane A membrane in the cochlea that contains the principal structures involved in auditory transduction.

inner hair cell (IHC) One of the two types of receptor cells for hearing in the cochlea.

outer hair cell (OHC) One of the two types of receptor cells for hearing in the cochlea.

stereocilium A relatively stiff hair that protrudes from a hair cell in the auditory or vestibular system.

tectorial membrane A structure in the cochlear duct.

The hair cells transduce movements of the basilar membrane into electrical signals

Each human ear contains two sets of sensory cells within the organ of Corti: a single row of about 3500 **inner hair cells** (**IHCs**; called *inner* because they are closer to the central axis of the coiled cochlea) and about 12,000 **outer hair cells** (**OHCs**) in three rows (see Figure 9.1*d*). The IHCs are flask-shaped, and the OHCs are cylindrical, with a diameter of approximately 5 μm and a length of 20 to 70 μm.

From the upper end of each hair cell protrude tiny hairs whose length ranges from 2 to 6 μm (Figure 9.1*e*). Each hair cell has 50 to 200 of these relatively stiff hairs, called **stereocilia** (singular *stereocilium*; from the Greek *stereos*, "solid," and the Latin *cilium*, "eyelid") or simply *cilia*. The heights of the stereocilia increase progressively across the hair cell, so the tops approximate an inclined plane. Atop the organ of Corti is the **tectorial membrane** (see Figure 9.1*d*). The stereocilia of the OHCs extend into indentations in the bottom of this membrane.

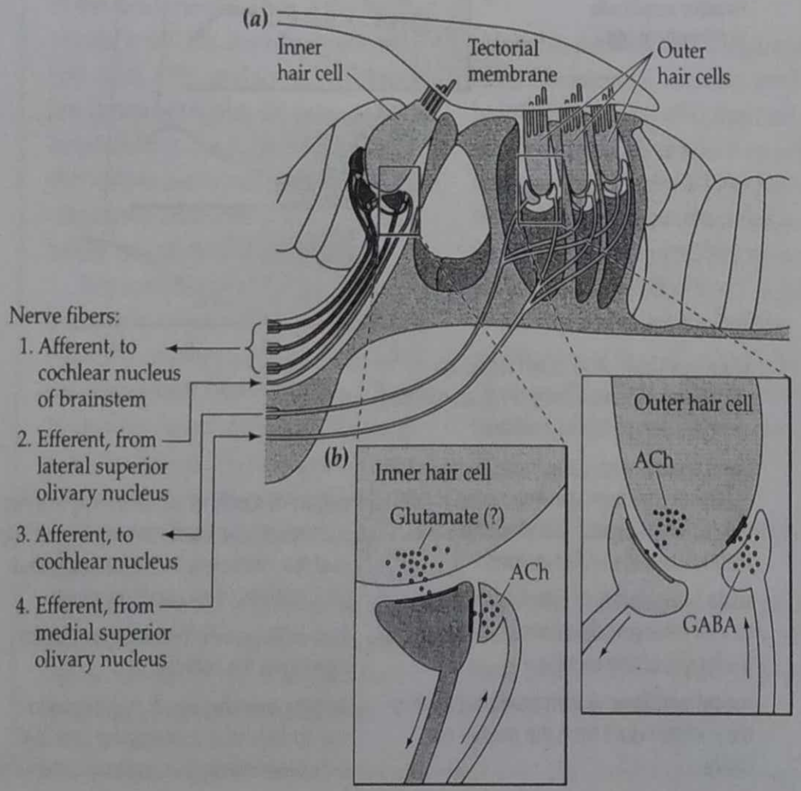
Auditory nerve fibers contact the base of the hair cells (see Figure 9.1*e*). The organ of Corti has four kinds of synapses and nerve fibers. Two of these (1 and 3 in **Figure 9.3*a***) are afferents that convey messages from the hair cells to the brain; the other two (2 and 4 in Figure 9.3*a*) are efferents that convey messages from the brain to the hair cells. Different synaptic transmitters are active at each type of synapse (**Figure 9.3*b***) (Eybalin, 1993). Each IHC is associated with 16 to 20 auditory nerve fibers; relatively few nerve fibers contact the many OHCs. In fact, the afferent nerve fibers running from the IHCs account for 90% to 95% of the afferent auditory fibers, and give rise to the perception of sound. Thus, mutant mice that lack IHCs but have normal OHCs are deaf (Deol and Gluecksohn-Waelsch, 1979). The auditory afferents from the cochlea synapse on neurons in the cochlear nuclei of the pons.

The OHCs don't detect sound; they fine-tune the organ of Corti so that the IHCs can do that job. Controlled by the brain via their efferent nerve fibers, the OHCs can change their length (Zheng et al., 2000), thereby influencing the mechanics of the cochlea. Changes in length of the OHCs can stiffen or relax segments of the basilar membrane and thus actively sharpen its tuning to different frequencies, as we will see later in this chapter (Ashmore, 1994). The IHCs also receive efferent messages, probably to inhibit some of the input from loud sounds.

How do hair cells turn movement into neural activity? Through the mechanisms we have already discussed, sounds induce vibrations of the basilar membrane. These vibrations bend the hair cell stereocilia that are inserted into the tectorial membrane (see Figure 9.1*d*). Very small displacements of hair bundles cause rapid changes in ionic channels of the stereocilia. These changes initiate excitation of the hair cells and then of the afferent axons (Hudspeth, 1992).

The ion channels in the stereocilia are gated by mechanical energy, as are those in touch receptors (see Chapter 8), but the gates in the channels for hearing are specialized for extremely rapid response: they can open and close thousands of times per second. This rapidity rules out the use of second messengers, which are found in receptors for smell, taste, and sight (as we'll see later in this chapter and in Chapter 10).

9.3 Auditory Nerve Fibers and Synapses in the Organ of Corti (*a*) The inner and outer hair cells form synaptic connections to and from the brain. (*b*) Different synaptic transmitters are hypothesized to be active at the synapses of inner and outer hair cells in the organ of Corti.

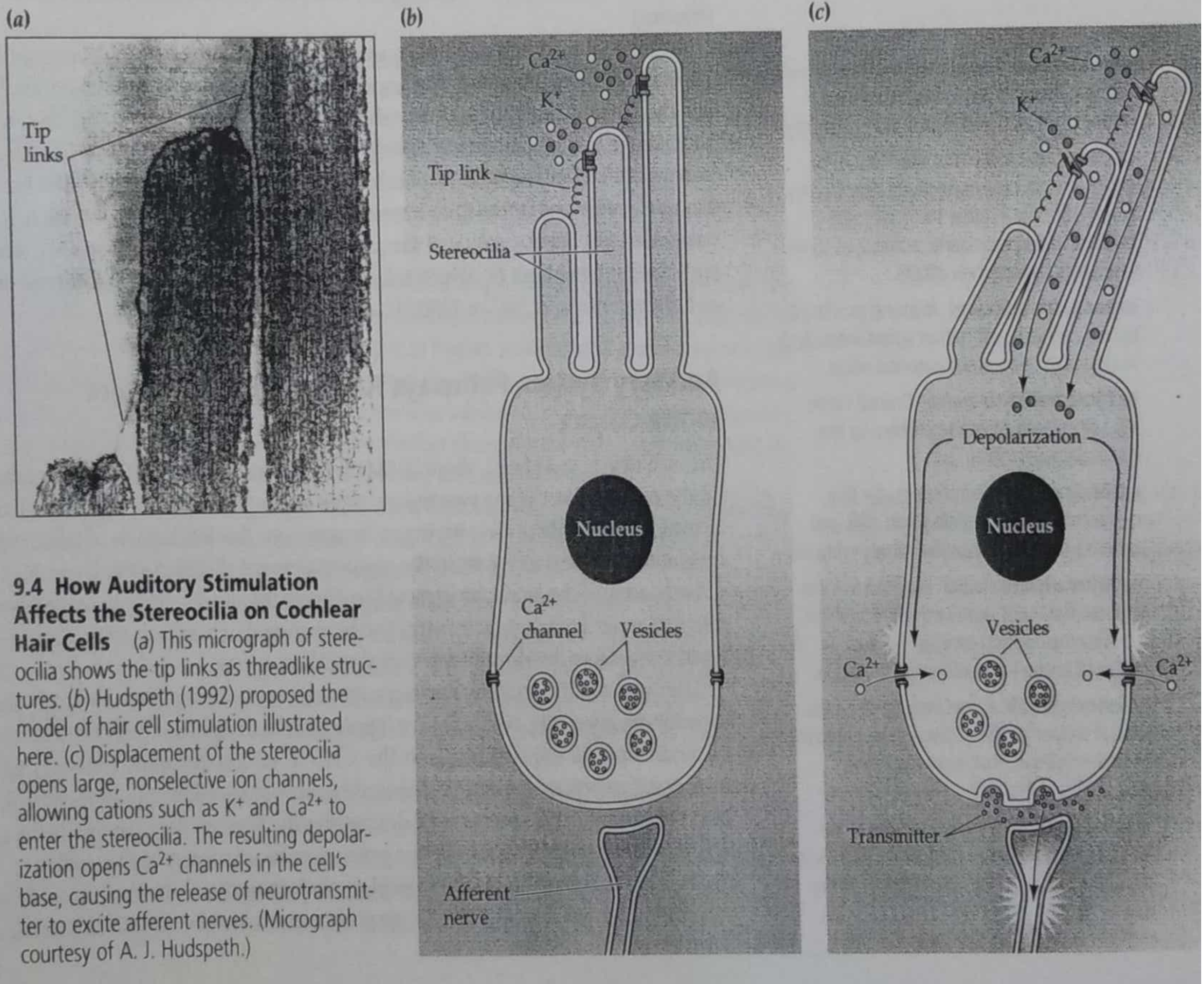

(*a*)
Inner hair cell
Tectorial membrane
Outer hair cells
Nerve fibers:
1. Afferent, to cochlear nucleus of brainstem
2. Efferent, from lateral superior olivary nucleus
3. Afferent, to cochlear nucleus
4. Efferent, from medial superior olivary nucleus
(*b*)
Inner hair cell
Glutamate (?)
ACh
Outer hair cell
ACh
GABA

Current estimates suggest that each hair cell has only about 100 ion channels, about one or two per stereocilium, located toward the tops of the cilia. Fine, threadlike fibers called **tip links** run along the tips of the stereocilia (**Figure 9.4a**). These tip links play a key role in the generation of hair cell potentials. Sounds that cause the stereocilia to sway, even only very slightly, increase the tension on the elastic tip links and pop open the ion channels to which they are attached (Hudspeth, 1997; Hudspeth et al., 2000). The channels snap shut again in a fraction of a millisecond as the hair cell sways back (**Figure 9.4*b* and *c***). The ion channels of stereocilia resemble trapdoors or portholes and appear to consist of a channel protein, called *TRPA1* (for *transient receptor potential type A1*) (Corey et al., 2004), that contains a springlike component called *ankyrin*—so in a real sense, a stereocilium ion channel is spring-loaded with a hair trigger.

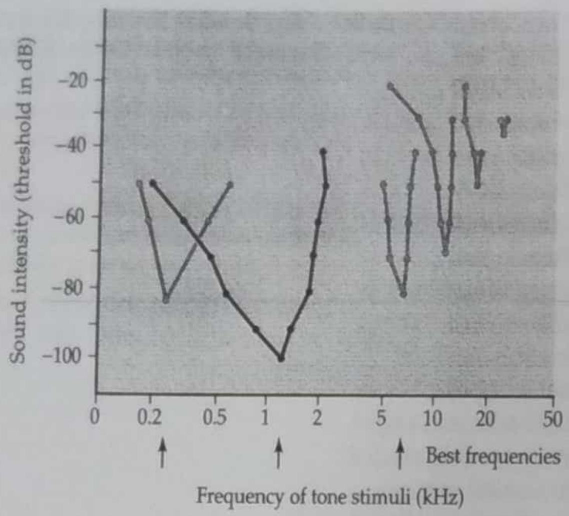
tip link A fine, threadlike fiber that runs along and connects the tips of stereocilia.

Opening of the channels allows an inrush of potassium (K^+) and calcium (Ca^{2+}) ions and rapid depolarization of the entire hair cell. This initial depolarization leads to a rapid influx of calcium ions (Ca^{2+}) at the *base* of the hair cell, which causes synaptic vesicles there to fuse with the presynaptic membrane and release their chemical contents—thought to be the synaptic transmitter glutamate—from the base of the hair cell, and stimulate the afferent nerve fiber (see Figure 9.4c).

The ion pores in the cilia are large and do not discriminate different kinds of ions. They even let small organic molecules pass through, which is why some drugs, such as aspirin and antibiotics, can impair hair cells by attacking their mitochondria. Susceptibility to this kind of damage of the receptor is inherited maternally, as are the mitochondria themselves.



9.4 How Auditory Stimulation Affects the Stereocilia on Cochlear Hair Cells (a) This micrograph of stereocilia shows the tip links as threadlike structures. (*b*) Hudspeth (1992) proposed the model of hair cell stimulation illustrated here. (*c*) Displacement of the stereocilia opens large, nonselective ion channels, allowing cations such as K^+ and Ca^{2+} to enter the stereocilia. The resulting depolarization opens Ca^{2+} channels in the cell's base, causing the release of neurotransmitter to excite afferent nerves. (Micrograph courtesy of A. J. Hudspeth.)



9.5 Examples of Tuning Curves of Auditory Nerve Cells These curves are obtained by measurement of neural responses to sounds of different intensities and frequencies. Because they represent threshold measurements, the *lowest* point on each curve corresponds to that neuron's preferred frequency. Illustrated here are responses of six neural units recorded from the auditory nerve of the cat. (After Kiang, 1965.)

Active electromechanical processes in the cochlea enhance frequency discrimination

Humans can discriminate between sounds that differ in frequency by just 2 Hz. Early studies of the **tuning curves** of single auditory nerve fibers, recorded electrically from the vestibulocochlear (VIII) nerve, revealed much more precise tuning than Békésy had found in his measurements of the physical tuning of the basilar membrane. The fact that the basic physical characteristics of the basilar membrane cannot account for the sharpness of tuning found in the auditory nerve indicated that an additional sharpening process must be at work. We now know that the cochlea itself has a remarkable electromechanical system for enhancing its tuning.

We mentioned earlier that OHCs show the surprising property of changing length when they are stimulated electrically—an electromechanical response (Brownell et al., 1985). Hyperpolarization causes the OHCs to lengthen; depolarization causes them to shorten. These changes, which amount to as much as 4% of the length of the cell, occur almost instantaneously. Investigators hypothesize that these mechanical responses of the OHCs serve as a **cochlear amplifier**, amplifying the movements of the basilar membrane in some regions and damping basilar membrane movements in other regions. This active and ongoing modulation of the basilar membrane sharpens the tuning of the cochlea (Ashmore, 1994; Hubbard, 1993). A surprising consequence of this mechanical process is that the cochlea itself produces sounds—called **otoacoustic emissions**—both spontaneously and in response to environmental noises. (Otoacoustic emissions are discussed in more detail on the website in **A Step Further: The Ears Emit Sounds as Part of the Hearing Process**.)

Each auditory neuron responds to a very precise frequency at its threshold, but for more-intense stimuli the neuron responds to a broader range of frequencies. For example, the fiber whose responses are shown in red in **Figure 9.5** has its *best frequency* at 1200 Hz; that is, it responds to a very weak tone at 1200 Hz. When sounds are 20 dB stronger, however, the fiber responds to any frequency from 500 to 1800 Hz. Thus, although an auditory nerve fiber transmits exclusively auditory information, it does not respond to just one frequency of stimulation. If the brain received a signal from only one such fiber, it would not be able to tell whether the stimulus was a weak tone of 1200 Hz or a stronger tone of 500 or 1800 Hz, or any frequency in between.

Auditory System Pathways Run from the Brainstem to the Cortex

On each side of your head, about 30,000 to 50,000 auditory fibers from the cochlea make up the auditory part of the **vestibulocochlear nerve** (cranial nerve VIII). Recall that most of these afferent fibers are carrying messages from the IHCs, each of which stimulates several nerve fibers. Input from the auditory nerve is distributed in a complex manner to both sides of the brain, as depicted in **Figure 9.6**. Each auditory nerve fiber divides into two main branches as it enters the brainstem. Each branch then goes to separate groups of cells in the dorsal and ventral **cochlear nuclei**.

The output of the cochlear nuclei also travels via multiple paths. One path goes to the **superior olivary nuclei**, which receive inputs from both right and left cochlear nuclei. This bilateral input is the first stage in the CNS at which *binaural* (two-ear) effects are processed; as you might expect, this mechanism plays a key role in localizing sounds by comparing the two ears, as we'll discuss shortly. Several other parallel paths converge on the **inferior colliculi**, which are the primary auditory centers of the midbrain. Outputs of the inferior colliculi go to the **medial geniculate nuclei** of the thalamus. At least two different pathways from the medial geniculate extend to several auditory cortical areas.

tuning curve A graph of the responses of a single auditory nerve fiber or neuron to sounds that vary in frequency and intensity.

cochlear amplifier The mechanism by which the cochlea is physically distorted by outer hair cells in order to "tune" the cochlea to be particularly sensitive to some frequencies more than others.

otoacoustic emission A sound produced by the cochlea itself, either spontaneously or in response to an environmental noise.

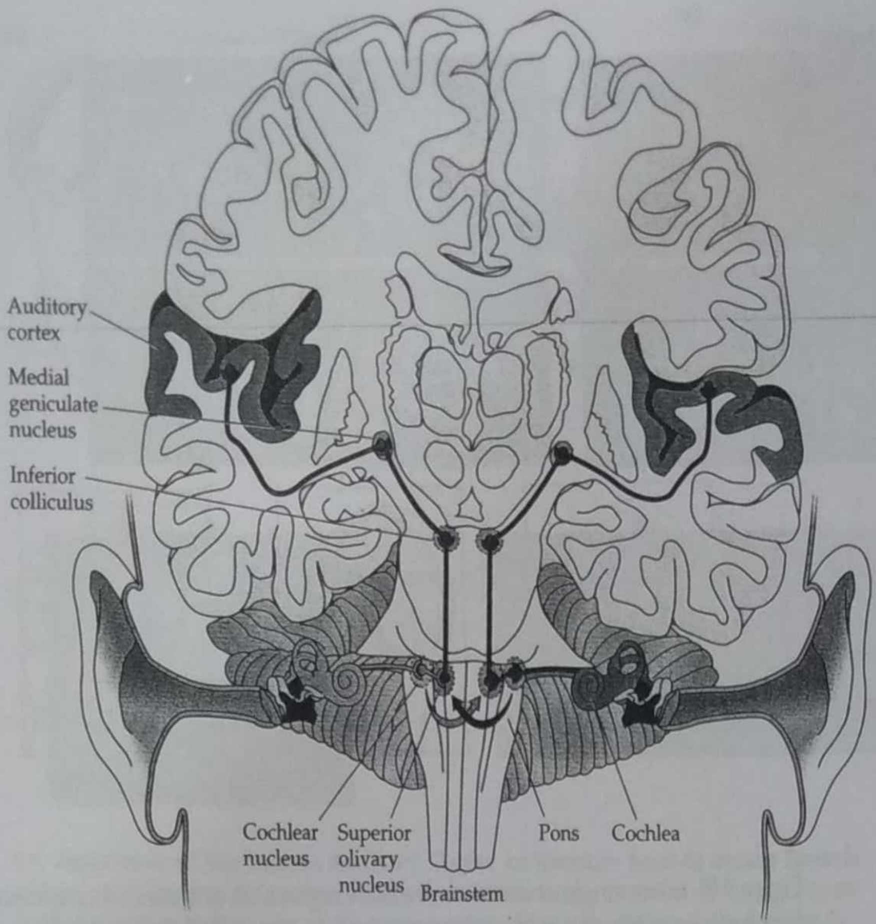
vestibulocochlear nerve Cranial nerve VIII, which runs from the cochlea to the brainstem auditory nuclei.

cochlear nuclei Brainstem nuclei that receive input from auditory hair cells and send output to the superior olivary complex.

superior olivary nuclei Brainstem nuclei that receive input from both right and left cochlear nuclei, and provide the first binaural analysis of auditory information.

inferior colliculi Paired structures on the dorsal surface of the midbrain, caudal to the superior colliculi, that receive auditory information.

medial geniculate nuclei Nuclei in the thalamus that receive input from the inferior colliculus and send output to the auditory cortex.



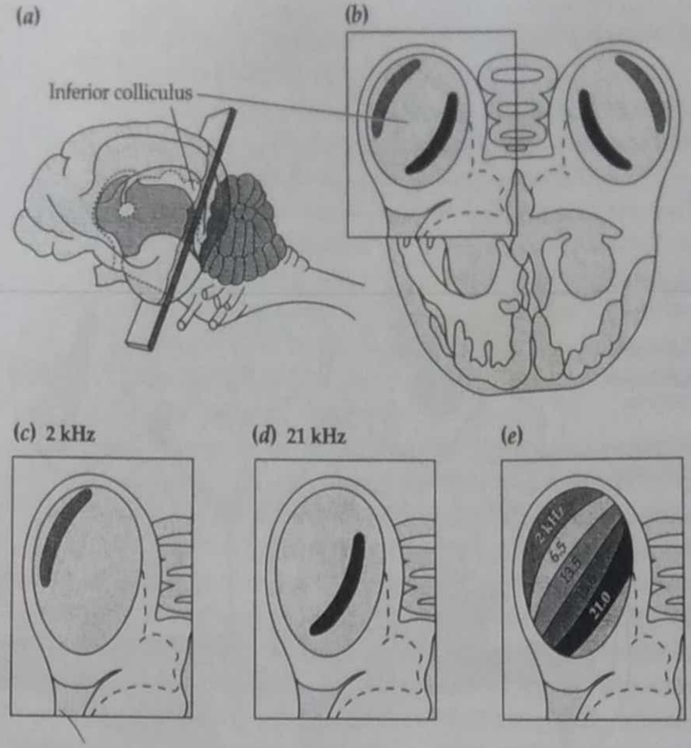
9.6 Auditory Pathways of the Human Brain This view from the front of the head shows the first binaural afferent interactions in the brainstem. Most (but not all) of the information from each ear projects to the cortex on the opposite side of the brain, as illustrated here by the colors of the projections to the medial geniculate and cortex.

Throughout the auditory pathways, neuronal response is frequency-sensitive, like the vestibulocochlear nerve fibers that we discussed earlier (see Figure 9.5). This ability to discriminate frequencies is even sharper at higher stations of the auditory nervous system. At the medial geniculate nucleus and the auditory cortex, not only are neurons excited by certain frequencies, but they are also inhibited by neighboring frequencies. This interplay of excitation and inhibition further sharpens the frequency responses, allowing us to discriminate very small frequency differences.

At every level of the auditory system, from cochlea to auditory cortex, auditory neurons display **tonotopic organization**; that is, they are spatially arranged in an orderly map according to the auditory frequencies to which they respond. Tonotopic organization can be demonstrated by the mapping of auditory brain regions using 2-deoxyglucose (2-DG), as shown in **Figure 9.7**. Following 2-DG injection, an animal is exposed to a tone of a particular frequency. Because 2-DG is taken up like glucose by neurons, but not metabolized, the most-active neurons take up the most 2-DG. Postmortem processing of 2-DG distribution reveals which cells were most active when the stimulus frequency was presented.

In humans, PET and fMRI studies show that stimulation with pure tones or noise activates chiefly the primary auditory cortex on the superior temporal lobe (**Figure 9.8a**). (The organization of auditory cortical areas in other species is described on the website in **A Step Further: The Auditory Cortical Regions of Many Species Show Tonotopic Organization**.) Speech activates this and other, more specialized auditory areas (see

tonotopic organization A major organizational feature in auditory systems in which neurons are arranged as an orderly map of stimulus frequency, with cells responsive to high frequencies located at a distance from those responsive to low frequencies.



9.7 Mapping Auditory Frequencies in the Cat Inferior Colliculus (a) This lateral view of the cat brain shows the plane of the transverse section through the inferior colliculus shown in part *b*. (c, d) Locations of the cells labeled with 2-DG via (c) 2000-Hz stimulation and (d) 21,000-Hz stimulation are indicated here by blue and red, respectively. (e) Complete tonotopic mapping shows the range of frequencies that can stimulate the cat's auditory system. (After Serviere et al., 1984.)

Figure 9.8). Interestingly, at least some of these regions are activated when normal subjects try to lip-read—that is, to understand someone by watching that person's lips without auditory cues (L. E. Bernstein et al., 2002; Calvert et al., 1997); this result suggests that the auditory cortex integrates other, nonauditory, information with sounds.

Two Main Theories Describe How We Discriminate Pitch

Most of us can discriminate very small differences in frequency of sound over the entire audible range—from 20 Hz to 15,000 or even 20,000 Hz. The ability to detect a change in frequency is usually measured as the **minimal discriminable frequency difference** between two tones. The detectable difference is about 2 Hz for sounds up to 2000 Hz; above these frequencies it grows larger.

Note that *frequency* and *pitch* are not synonymous terms. *Frequency* describes a physical property of sounds; *pitch* relates solely to the subjective sensory experience of sounds (see Box 9.1). This is an important distinction because frequency is not the sole determinant of perceived pitch (at some frequencies, higher-intensity sounds may seem higher-pitched), and changes in pitch do not precisely parallel changes in frequency.

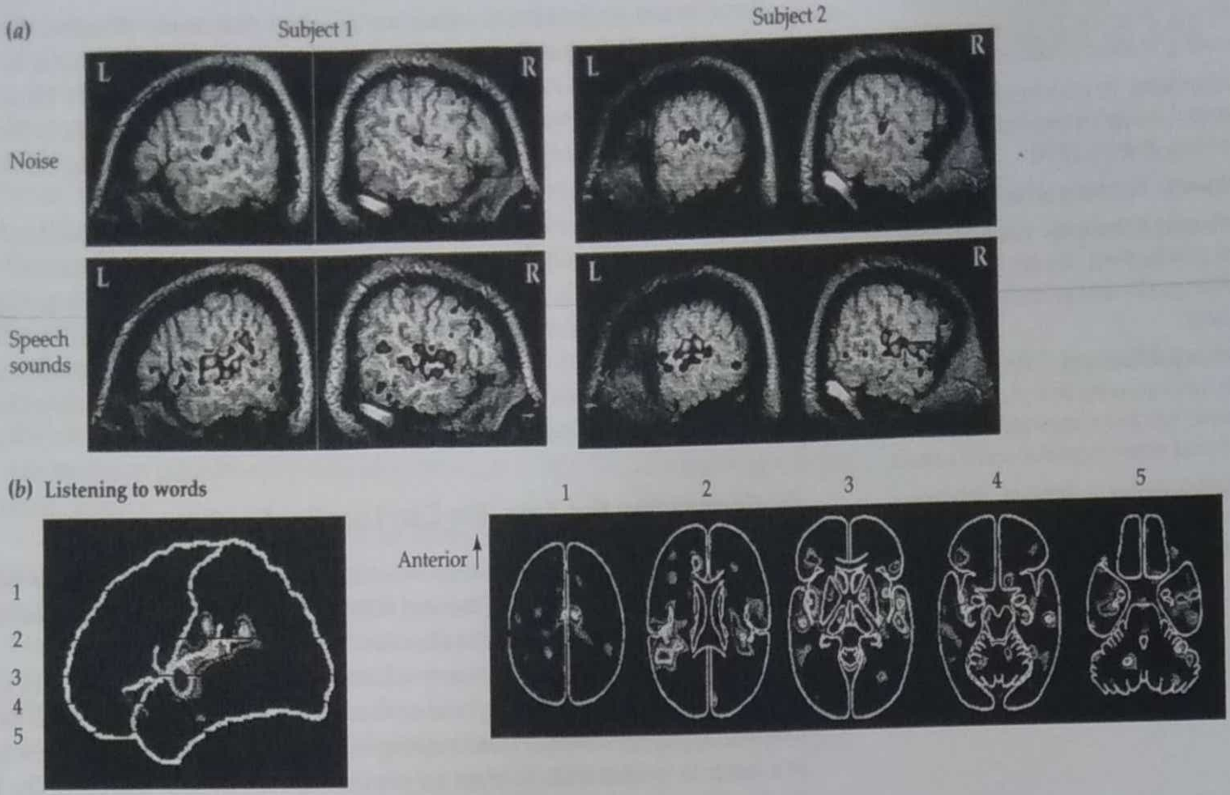
How do we account for the ability to discriminate pitches? Two main theories have been offered. One, described as **place theory**, argues that pitch is encoded in the physical location of the activated receptors along the length of the basilar membrane: activation of receptors near the base of the cochlea (which is narrow and responds to high frequencies) signals *treble*, and activation of receptors nearer the apex (which is wide and responds to low frequencies) signals *bass*. The alternative idea, **volley theory**, proposes that frequency of auditory stimuli is directly encoded in the firing pattern of auditory neurons: for example, a 500-Hz sound might cause some neurons to fire 500 action potentials per second. In such cases the firing of the action potential is *phase-locked* to the stimulus; that is, it occurs at a particular portion of the cycle. Such a phase-locked representation can be accomplished more accurately by several cells than by a single cell—hence the term *volley*, as in a volley of action potentials.

Are these views—place and volley theories—necessarily antagonistic? No. In fact, the contemporary view of pitch perception incorporates both perspectives:

minimal discriminable frequency difference The smallest change in frequency that can be detected reliably between two tones.

place theory A theory of frequency discrimination stating that pitch perception depends on the place of maximal displacement of the basilar membrane produced by a sound.

volley theory A theory of frequency discrimination that emphasizes the relation between sound frequency and the firing pattern of nerve cells.



9.8 Responses of the Human Auditory Cortex to Random Sounds versus Speech (a) Functional-MRI scans of the cerebral hemispheres show that pure tones or noise (*top*) activate chiefly the primary auditory area on the superior aspect of the temporal lobe, while listening to speech sounds (*bottom*) activates other auditory cortical regions, as well as the primary auditory area. (*b*) Lateral (*left*) and horizontal (*right*) PET scans show that listening to words activates not only several regions of the cerebral cortex but also regions of the thalamus and the cerebellum. The numbered horizontal lines in the left-hand panel correspond to the levels of the horizontal sections in the right-hand panel. (Part *a* from Binder et al., 1994, courtesy of Jeffrey Binder; *b* from Posner and Raichle, 1994, courtesy of Marcus Raichle.)

1. As place theory predicts, a change in frequency is accompanied by a change in the region of maximal disturbance of the basilar membrane, as well as activation of associated auditory receptors. For complex sounds with components at several different frequencies, the cochlea accomplishes a sort of Fourier analysis (see Box 9.1), with the different frequencies mapped as peaks of vibration at different places along the basilar membrane. The accuracy of place representation of auditory frequency has improved over the course of evolution as the basilar membrane has lengthened and the number of hair cells and auditory nerve fibers has increased.
2. As volley theory predicts, temporal patterns of neural discharges appear to encode auditory frequencies. Direct recordings indicate that, for lower-frequency sounds, the frequency of action potentials often encodes the auditory frequency on a one-to-one basis. For higher-frequency sounds, the frequency of action potentials may instead encode an auditory frequency that is an integer multiple. Encoding a multiple, rather than one-to-one, frequency allows the auditory system to overcome the maximal neuronal firing rate of about 1000 action potentials per second. In general, volley coding is emphasized at the lower end of the hearing range, up to about 4000 Hz.

So the frequency properties of a sound are coded in two ways: (1) according to the distribution of excitation among cells—that is, place coding or tonotopic representation—and (2) according to the temporal pattern (volley) of discharge in cells projecting to the auditory cortex.

ultrasound High-frequency sound; in general, above the threshold for human hearing, at about 20,000 Hz.

infrasound Very low frequency sound; in general, below the threshold for human hearing, at about 20 Hz.

binaural Pertaining to two ears.

intensity differences Perceived differences in loudness between the two ears, which can be used to localize a sound source.

latency differences Differences between the two ears in the time of arrival of a sound, which can be employed by the nervous system to localize sound sources.

duplex theory A theory of pitch perception that combines place theory and volley theory.

Some species are sensitive to sounds with very high frequencies (**ultrasound**) or very low frequencies (**infrasound**), and make use of them in special ways. For example, many species of bats produce loud vocalizations, in the range of 50,000 to 100,000 Hz, and listen to the echoes reflected back from objects in order to navigate and hunt in the dark. Their extraordinary sensitivity and accuracy is conferred by elaborate adaptations that adorn their bodies and brains.

At the other end of the spectrum, homing-pigeon races are severely disrupted if the birds encounter the sonic-boom shock wave of a supersonic jet (an infrasound pulse that can travel hundreds of miles), suggesting that the pigeons use infrasound cues to establish a navigational map (Hagstrum, 2000). Tigers may use infrasound to add impact to their roars (Walsh et al., 2003), and infrasound experimentally inserted into concerts heightens the music's emotional effect on human listeners, but it's not yet known how we detect infrasound.

By Comparing the Ears, We Can Localize Sounds

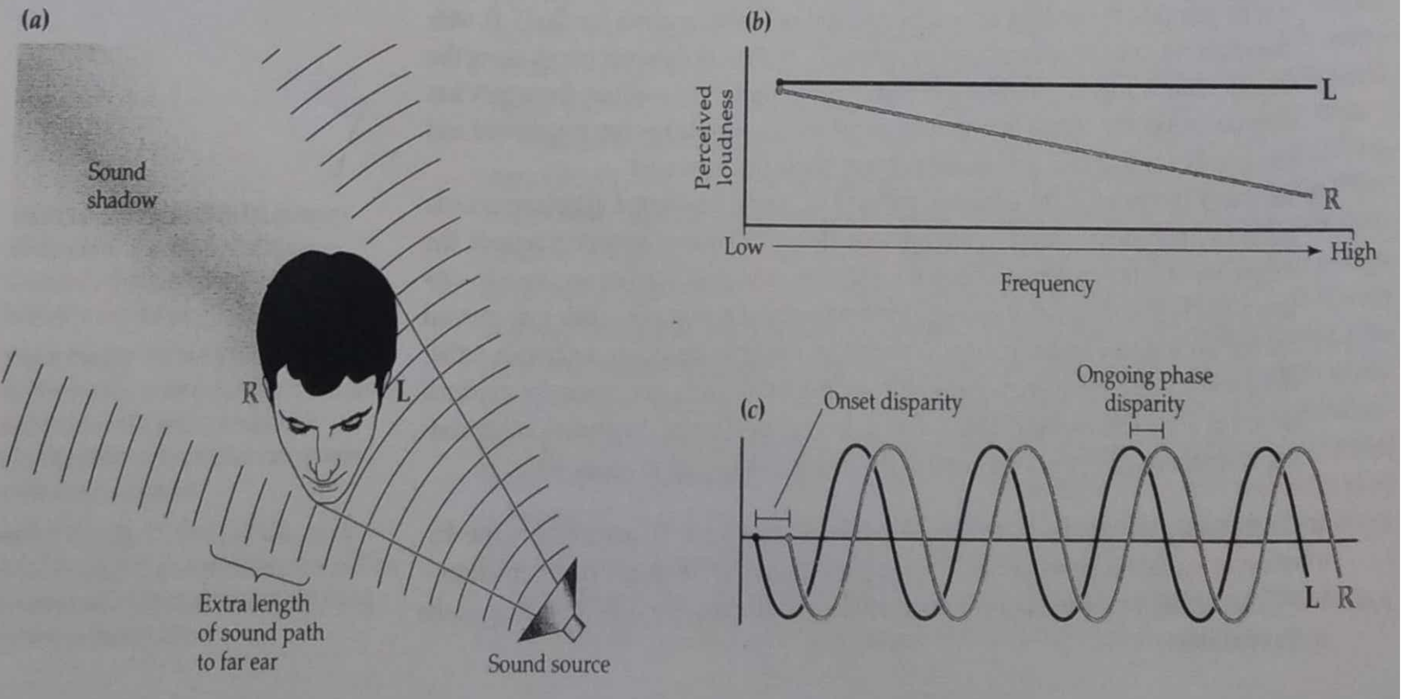
Normally we can locate the position of a sound source with great accuracy (within about 1°) by analyzing **binaural** (two-ear) differences in the sound. Two kinds of binaural cues signal the location of a sound source.

Intensity differences are differences in loudness at the two ears. In humans, intensity differences arise because the head casts a sound shadow, blocking sounds located to one side (off-axis sounds) from reaching both ears with equal loudness (this is less of a factor in species with different ear placement, such as dogs and cats). The head shadow is most pronounced for higher-frequency sounds. Low-frequency sounds have longer sound waves that reach around the head.

Latency differences are differences between the two ears in the time of arrival of sounds. They arise because one ear is always a little closer to an off-axis sound than is the other ear. Two kinds of latency differences are present in a sound: *onset disparity*, which is the difference between the two ears in hearing the beginning of the sound; and *ongoing phase disparity*, which is the continuous mismatch between the two ears in the arrival of all the peaks and troughs that make up the sound wave (these cues are illustrated in **Figure 9.9**).

We now know that sound localization involves processing of both intensity differences and latency differences; this is known as the **duplex theory**. At low frequencies, no matter where sounds are presented in *azimuth* (horizontally around your head), there are virtually no intensity differences between the ears. For these frequencies, differences

9.9 Cues for Binaural Hearing
(*a*) The two ears receive somewhat different information from sound sources located to one side or the other of the observer's midline. (*b*) The head blocks frequencies greater than 1000 Hz, producing binaural differences in sound intensity. The resulting differences in perceived intensity are greater at higher frequencies. (*c*) Sounds also take longer to reach the more distant ear, resulting in binaural differences in time of arrival. *Onset disparity* is the latency difference between the two ears for the beginning of a sound. *Ongoing phase disparity* is the difference between the ears for arrival of the peaks and troughs of the sound wave.

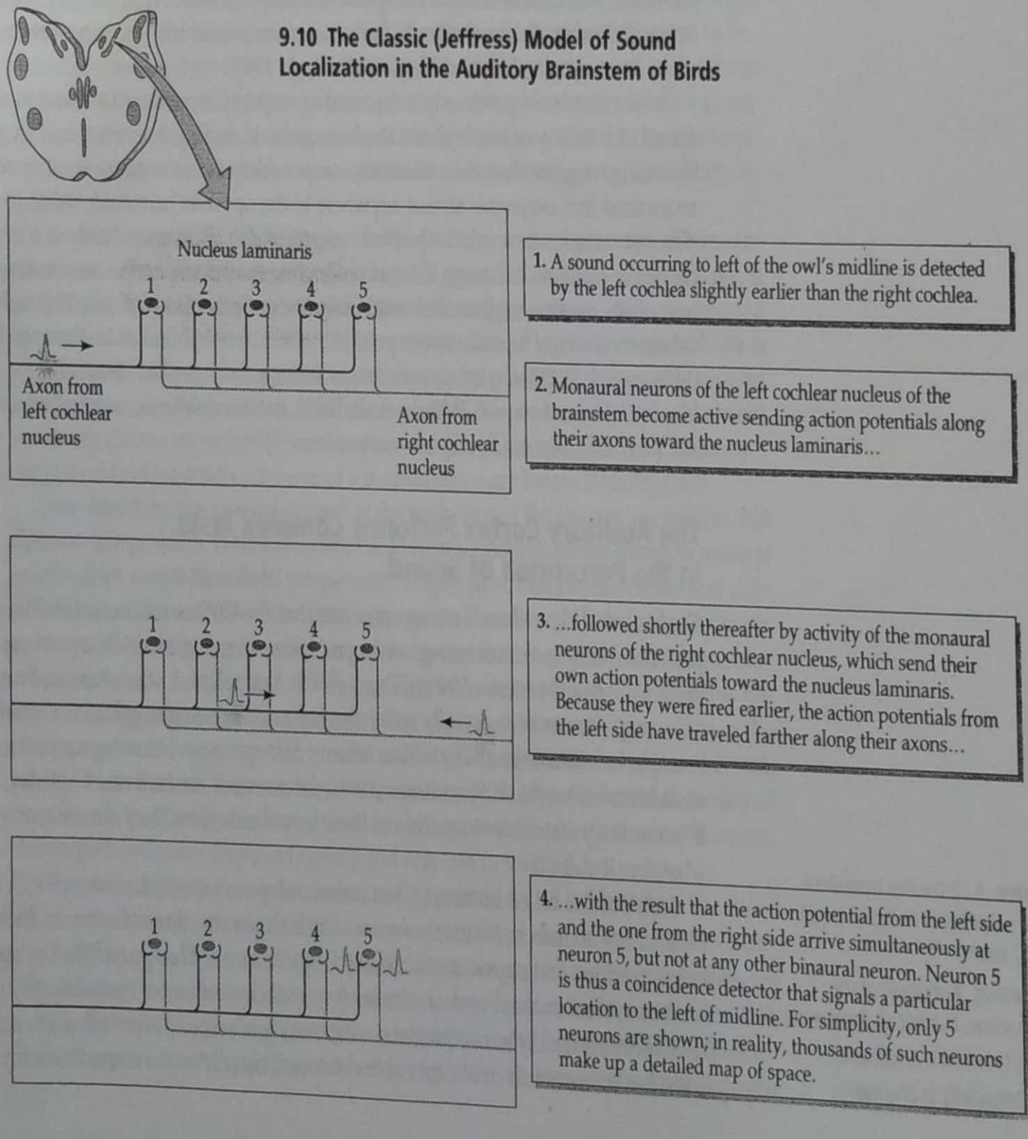


in times of arrival are the principal cues for sound position (and at very low frequencies, neither cue is much help; this is why you can place the subwoofer of an audio system anywhere you want). At higher frequencies, however, the sound shadow cast by the head produces significant binaural intensity differences. Of course, you can't perceive which types of processing you're relying on for any given sound; in general, we are aware of the *results* of neural processing but not the processing itself.

What brain systems analyze binaural cues? Tympanate (eardrum) hearing appears to have evolved independently in birds and mammals (and others), and these groups of animals have evolved different solutions to particular auditory problems, such as the localization of sounds—a nice example of convergent evolution (see Chapter 6). Both birds and mammals have highly specialized brainstem mechanisms that receive information from the two ears, and they use arrays of bipolar neurons to derive sound location from the left and right auditory signals. These bipolar neurons are capable of making very precise timing calculations by comparing the inputs to their two dendrites (Agmon-Snir et al., 1998).

In birds, the organization of neurons within the primary sound localization nucleus (called the *nucleus laminaris*) constitutes an auditory map of space. In this model, originally proposed by Jeffress (1948), each binaural neuron of the nucleus laminaris functions as a **coincidence detector** and is maximally excited by a particular latency difference between inputs from the two ears, corresponding to a particular place in space (**Figure 9.10**). This map is further developed at higher levels, especially the *tectum* (equivalent to the mammalian inferior colliculus), which contains a complete map of space.

coincidence detector A device that senses the co-occurrence of two events.


Nucleus laminaris
1
2
3
4
5
Axon from left cochlear nucleus
Axon from right cochlear nucleus

9.10 The Classic (Jeffress) Model of Sound Localization in the Auditory Brainstem of Birds

1. A sound occurring to left of the owl's midline is detected by the left cochlea slightly earlier than the right cochlea.

2. Monaural neurons of the left cochlear nucleus of the brainstem become active sending action potentials along their axons toward the nucleus laminaris...

3. ...followed shortly thereafter by activity of the monaural neurons of the right cochlear nucleus, which send their own action potentials toward the nucleus laminaris. Because they were fired earlier, the action potentials from the left side have traveled farther along their axons...

4. ...with the result that the action potential from the left side and the one from the right side arrive simultaneously at neuron 5, but not at any other binaural neuron. Neuron 5 is thus a coincidence detector that signals a particular location to the left of midline. For simplicity, only 5 neurons are shown; in reality, thousands of such neurons make up a detailed map of space.

9.11 All Ears Like other mammals, including humans, the ridges and valleys of this bat's outer ear produce precise changes, called *spectral filtering*, in the sounds being funneled into the ear. This process provides additional cues about the location of a sound source.

Mammals apparently do things quite differently. The **superior olive** is the primary sound localization nucleus in the mammalian brain, and its two main divisions serve different functions. The *lateral superior olive* processes intensity differences. The *medial superior olive* (*MSO*) processes latency differences, but in contrast to birds, the MSO does not appear to contain a map of auditory space. Instead, sound location is encoded by the relative activity of the *entire* left MSO compared with the *entire* right MSO (Grothe, 2003; McAlpine et al., 2001).

So, for example, a sound on the midline would activate the left and right MSO equally, and the two signals would effectively cancel each other out. But a sound on the right would produce more excitation of the left MSO than the right MSO, and the converse would be true for sounds on the left. The bigger the difference between the left and right MSO is, the farther the sound source is from the midline. This disparity is passed along for further processing at other levels of the auditory system, such as the inferior colliculus.

The structure of the external ear provides yet another sort of localization cue. As we mentioned earlier, the hills and valleys of the external ear selectively reinforce some frequencies in a complex sound and diminish others. This process is known as **spectral filtering**, and the frequencies that are affected depend on where the sound originates (**Figure 9.11**) (Kulkarni and Colburn, 1998).

The relationship between spectral cues and location is learned and calibrated during development. Spectral cues provide critical information about *elevation* (vertical localization), and are especially important for sounds located on the midline, where there are no intensity or latency differences between the ears. In fact, people who are deaf in one ear can utilize **monaural** (one-ear) spectral cues to localize sounds to some extent. Similarly, researchers can place a speaker directly in the ear canal and, by varying the spectral filtering of natural sounds, fool a person or animal into believing that the sound came from a particular point in space (Xu et al., 1999).

As we discussed previously, neurons that respond to auditory localization are also found at a variety of levels above the brainstem, including the cortex, and single-cell recordings suggest that their selectivity varies widely. Some auditory neurons respond to a sound that originates almost anywhere in the opposite hemifield. Other, location-sensitive neurons have relatively small receptive fields that respond only to sounds at a particular location. Although there is no discrete spatial map in the mammalian auditory cortex, models suggest that combining the receptive fields of only 128 such cortical neurons would be sufficient to predict the source of a sound as well as cats do (Furukawa et al., 2000). Orchestra conductors are especially good at identifying the spatial location of sound sources (Münte et al., 2001), presumably because of extensive practice ("Mr. Donini, could you *please* play in tune?").

The Auditory Cortex Performs Complex Tasks in the Perception of Sound

The historical view of auditory function was that the various subcortical auditory areas performed only basic processing, serving mostly as stepping-stones in a pathway to the auditory cortex (Masterton, 1993). The cortex, it was believed, was where auditory sensation and discrimination really arose. But behavioral testing suggested otherwise; for example, cats retain the ability to discriminate different tones following surgical removal of auditory cortex (M. R. Rosenzweig, 1946; for a review, see Neff and Casseday, 1977). If the auditory cortex is not involved in these basic kinds of auditory discrimination, then what *does* it do?

Early studies relied on simple, but unnatural, pure tones (Masterton, 1993, 1997). Most of the sounds in nature, however—such as vocalizations of animals, footsteps, snaps, crackles, and pops—contain many frequencies and change rapidly. The auditory nervous system evolved to deal with such sounds. Indeed, most central auditory neurons habituate rapidly to continuous sound, ceasing to respond after only a few milliseconds, but brief sounds or abrupt onsets of sound usually evoke responses from many

superior olive A distinctive brainstem nucleus that contributes to the binaural processing of sounds.

spectral filtering Alteration of the amplitude of some, but not all, frequencies in a sound.

monaural Pertaining to one ear.

neurons, from the cochlear nuclei to the auditory cortex. Ablation of the auditory cortex in cats does impair discrimination of temporal *patterns* of sound (Neff and Casseday, 1977). Similarly, bilateral ablation of the auditory cortex in monkeys impairs their ability to discriminate species-specific vocalizations (Heffner and Heffner, 1989). So auditory cortex analyzes complex sounds encountered in everyday life.

There seem to be two main streams of auditory processing in cortex (Kaas and Hackett, 1999): a dorsal stream, involving the parietal lobe, may be concerned with spatial location of sounds; a ventral stream through the temporal lobe may analyze the various components of sounds (Romanski et al., 1999). Perhaps this distinction forms the basis of the *where* and *what* auditory processing streams; a similar processing scheme has been proposed for visual processing too (see Chapter 10).

Experience affects auditory perception and the auditory pathways

Aspects of auditory discrimination, and the neural circuits involved in hearing, change as we grow. At birth the human infant has diverse hearing abilities. Postnatal developments involve elaborate structural changes throughout auditory pathways. Accompanying these changes are progressive improvements in the perception of complex sounds, such as speech. Because the world after birth is filled with a complex array of sounds, it is reasonable to ask whether experience shapes or modulates the forming of connections in the auditory system.

One demonstration of the role of early auditory experience comes from studies of musicians (Pantev et al., 1998). In these studies the evoked brain activity from musicians and nonmusicians was identical in response to pure tones. But if, instead of pure tones, the more complex and musically relevant sounds from a piano were used, musicians displayed a greater brain response than did nonmusicians. Now, maybe these people became musicians because their brains were more responsive to complex tones to begin with. However, there was a significant correlation between the magnitude of brain response to piano tones and the age at which the musicians had begun studying music. The earlier the musician had begun her studies, the greater her brain response to piano tones, suggesting that early exposure to musical training affects brain auditory responsiveness.

Certainly there are big differences by adulthood: the portion of primary auditory cortex where music is first processed, called *Heschl's gyrus*, is more than twice as large in professional musicians as in nonmusicians, and more than twice as strongly activated by music (P. Schneider et al., 2002). Debate continues about whether musical ability is a specific and hardwired human trait, or just a happy by-product of systems that evolved for other purposes (Balter, 2004), but the existence of disorders in which people cannot accurately discern tunes (called **amusia**; from the Greek *amousia*, "want of harmony") suggests that at least the rudiments of a musical sense are innate (Münte, 2002).

Tone-deaf Tony, whom we described at the beginning of the chapter, exemplifies this dyslexia-like problem. Whereas most infants clearly understand the basics of musical relationships almost from birth, people with congenital amusia never develop that ability (Peretz and Hyde, 2003). Brain imaging suggests that the right inferior frontal gyrus is abnormal in amusia, containing less white matter than in people with normal music perception (K. L. Hyde et al., 2006), agreeing with earlier studies indicating that the right frontal region is important for perception of pitch. Interestingly, perception of the timing aspects of music (*rhythm*), may be unaffected in amusia (K. L. Hyde and Peretz, 2004). We assume that Tony was born with a problem that severely limited the ability of the relevant brain mechanisms, such as Heschl's gyrus and right inferior frontal cortex, to comprehend music (especially pitch) and respond to training.

The role of auditory experience in the development of sound localization is illustrated by observations in bilaterally deaf children who were fitted with different types of hearing aids (Beggs and Foreman, 1980). The children in one group were given a hearing aid that delivered the same sounds to both ears. In a second group children were fitted with a separate hearing aid for each ear so that they experienced binaural stimuli. When examined years later, the children who had been fitted with binaural hearing aids were

amusia A disorder characterized by the inability to discern tunes accurately.

9.12 The Role of Vision in Auditory Localization This young owl has had prisms fitted over its eyes to deviate vision by about 10° to the side. At first, the owl makes mistakes when reaching for a visual target, but eventually it learns to adapt to the prisms. The neurons in its tectum also adapt, so now neurons excited by a sound from a particular location in space are also excited by visual stimuli presented 10° to the left of that location. (Courtesy of Eric Knudsen.)

able to localize sounds with significantly greater accuracy than the children who had experienced comparable overall levels of sounds but had been deprived of dichotic stimuli.

Auditory systems are calibrated through polymodal integration

In Chapter 8 we described the propensity of some brain regions to respond to inputs originating in two or more different sensory systems; we refer to this process as **polymodal**, or **multisensory**, integration. Experimental data indicate that information from other sensory modalities fine-tunes the accuracy of auditory systems.

Eric Knudsen et al. (1984) have performed elegant studies using an especially acute binaural perceiver: the barn owl. When hunting, owls use both arrival differences and intensity differences to accurately localize sounds at night (Peña and Konishi, 2000). Cells of the avian tectum are arranged in a roughly spherical map of space (Knudsen, 1984; Knudsen and Konishi, 1978). In the owl tectum, both auditory *and* visual space are represented, and the maps for the two senses overlap very closely (Knudsen, 1982). In fact, most cells in the owl tectum are polymodal: they respond to both auditory and visual stimuli, and it is thought that this close alignment of auditory and visual maps of space helps guide behavioral responses toward stimuli.

To assess the impact of early experience on the development of these maps, investigators plugged one ear of adult and baby owls. As a result, the birds made large errors in localizing sounds, with responses shifted in the direction of the open ear—presumably because the sound was more intense in that ear, which would normally mean that it had come from that side. Adult animals never seemed to adjust to the ear plug, but owls younger than 8 weeks at the time of plugging slowly began to compensate.

It turns out that vision is a key mediator in recalibrating auditory localization: the compensation did not occur if the owls were deprived of vision; and, if they were fitted with prism glasses that deviated vision by 10° (**Figure 9.12**), the adjustment of auditory localization was matched to this visual error (Knudsen and Knudsen, 1985). Apparently the induced mismatch between the auditory and visual tectal maps provoked a remapping of auditory space in the baby owls that was no longer possible in the brains of the adult owls. These changes might arise either from structural modifications of growing neural circuits or from modulations of synaptic effectiveness (Knudsen, 1998). The tight integration of auditory and visual perception probably relates to higher-level mechanisms that direct attention to specific locations in the environment (Winkowski and Knudsen, 2006).

Although in owls only juveniles have auditory systems that can be remodeled through experience, the auditory areas of mammals and other birds show plasticity that persists into adulthood. So, for example, if adult monkeys are trained to discriminate sounds in order to receive a food reward for several months, the cortical representation for the training frequencies becomes substantially larger. Control subjects that just passively listen to the same tones do not show this response (Recanzone et al., 1993). Similarly, conditioning a guinea pig to tones of a particular frequency can cause cortical neurons to shift their response to favor that frequency (**Figure 9.13**) (N. M. Weinberger, 1998). This remodeling can occur very quickly, on the order of just a few minutes (Fritz et al., 2003), reflecting an adaptive ability to continually tune and retune the auditory cortex to detect biologically significant sounds.

Intriguingly, it seems that reward may be a potent contributor to remodeling of auditory cortex. Each day for 20 days, Bao et al. (2001) presented rats with tones paired with microstimulation of the ventral tegmental area (VTA). VTA stimulation activates the brain's dopamine-based reward system (see Chapter 4). The investigators subsequently found that cortical representations were greatly increased for tones that occurred shortly before—but not after—the VTA stimulation. From an evolutionary perspective this sort of mechanism is highly adaptive because it specifically shapes the cortex to respond to stimuli that have previously signaled a reward, often in some other sensory modality.

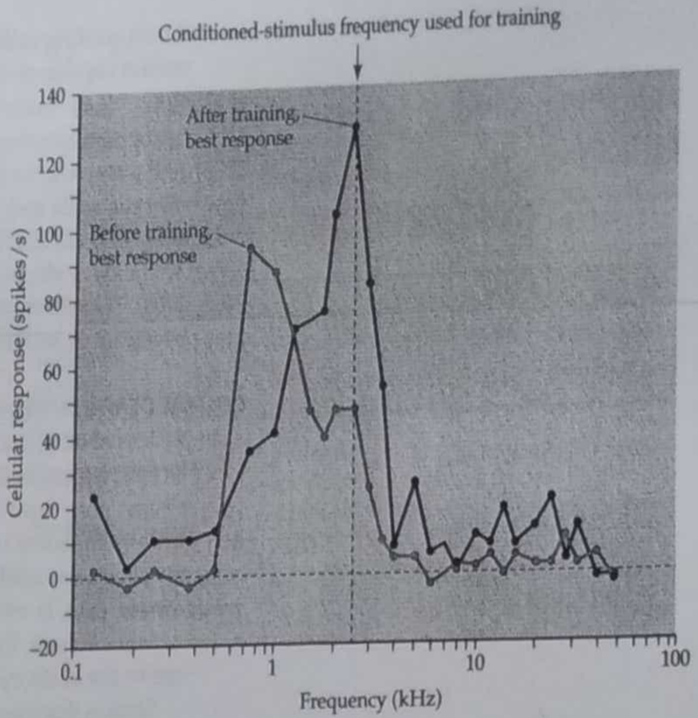
polymodal or multisensory Involving several sensory modalities.

Deafness Is a Major Disorder of the Nervous System

In the United States, about 11 million people (3.7% of the population) are categorized as either hard of hearing or profoundly deaf (Mitchell, 2006); the prevalence in other developed countries is probably similar. Auditory problems, which range in severity from occasional difficulties in speech perception to a complete inability to hear, can come about in several different ways.

There are three main causes of deafness

Many severe hearing impairments arise early in life and impair language acquisition. Others occur later in life as a consequence of environmental factors, such as exposure to loud sounds, infections, or side effects of certain drugs. There are three general categories of deafness—conduction, sensorineural, and central—and the latter two involve compromised neural function.



9.13 Long-Term Retention of a Trained Shift in Tuning of an Auditory Receptive Field Before training, the best frequency of the auditory cortex cell of an adult guinea pig that is represented on this graph was about 0.7 kHz. After training with a 1.1-kHz tone, the best frequency shifted to 1.1 kHz. After 2 and 4 weeks, the shift had remained stable. (From N. M. Weinberger, 1998.)

CONDUCTION DEAFNESS **Conduction deafness** arises when disorders of the outer or middle ear prevent vibrations produced by auditory stimuli from reaching the cochlea. In one common form of conduction deafness, the ossicles become fused and can no longer transmit sound vibrations effectively. Surgery to free up the ossicular chain is helpful in some cases. The nervous system is generally not involved in conduction deafness.

SENSORINEURAL DEAFNESS Metabolic dysfunctions, infections, exposure to toxic substances, trauma, exposure to loud sounds, and hundreds of hereditary disorders are all causes of **sensorineural deafness** (Pennisi, 1997). The end result is the same in each case: auditory nerve fibers are unable to become excited in a normal manner, and this hearing loss is usually permanent. Defects in certain genes governing hair cell structure and function are prominent causes of sensorineural deafness that is present from birth (Littlewood and Muller, 2000; E. D. Lynch et al., 1997). Mutations in a gene named *GJB2* may be responsible for as much as 50% of congenital or early-onset hearing impairment (Cryns and Van Camp, 2004); this gene encodes the protein connexin-26, which is involved in the formation of electrical synapses (*gap junctions*; see Chapter 3).

Drug-induced deafness sometimes results from the toxic properties of a group of antibiotics that includes streptomycin and gentamicin. The **ototoxic** (ear-damaging) properties of streptomycin were discovered when many patients that received it as treatment for tuberculosis subsequently developed cochlear and/or vestibular damage. In severe cases the hair cells of the cochlea were completely destroyed, producing total, irreversible loss of hearing.

Noise pollution and loud sounds—industrial noise, intense music, loud engines, and especially the firing of guns—can severely damage the cochlea in a short period of time. Once again, the hair cells suffer the brunt of the damage: in the affected part of the cochlea, the stereocilia appear shattered and broken, like a flattened forest. Loud sounds coupled with the use of some over-the-counter drugs, such as aspirin, can also have profound cumulative effects on hearing (McFadden and Champlin, 1990), reducing sensitivity to certain tones by up to 40 dB, and/or leading to the development of **tinnitus**, a sensation of noises or ringing in the ears (Brien, 1993).

Can damaged hair cells be regrown? Although fishes and amphibians produce new hair cells throughout life, mammals traditionally have been viewed as incapable of regenerating hair cells. This conclusion may have been too hasty, however. Through manipulation of certain genes, tissue cultures from the organ of Corti of young rats have been induced to produce new hair cells (Zheng and Gao, 2000). As in fishes and birds,

conduction deafness A hearing impairment that is associated with pathology of the external-ear or middle-ear cavities.

sensorineural deafness A hearing impairment that originates from cochlear or auditory nerve lesions.

ototoxic Toxic to the ears, especially the middle or inner ear.

tinnitus A sensation of noises or ringing in the ears.

the supporting cells packed around the hair cells of the mammalian organ of Corti do remain capable of dividing and differentiating into hair cells in adulthood (P. M. White et al., 2006). Insertion of a gene called *Atoh1* (also known as *Math1*) into isolated cochlear supporting cells causes those cells to turn into new hair cells (Kawamoto et al., 2003), and when a virus is used to insert *Atoh1* into the cochlea of deafened guinea pigs, new hair cells and some restoration of hearing are evident after about 8 weeks (Izumikawa et al., 2005). Alternatively, deletion of a gene called *Rb1* allows hair cells themselves to divide, providing new, functional hair cells in deafened cochlea (Sage et al., 2005, 2006). There is thus good reason to hope that a combination of these approaches may provide an effective gene therapy for deaf people, someday.

CENTRAL DEAFNESS **Central deafness** (hearing loss caused by brain lesions) is seldom a simple loss of auditory sensitivity. An example of the complexity of changes in auditory perception following cerebral cortical damage is **word deafness**, a disorder in which people show normal speech and hearing for simple sounds but cannot recognize spoken words. Some researchers have suggested that the basis of word deafness is an abnormally slow analysis of auditory inputs. Another example of central deafness is **cortical deafness**, in which patients have difficulty recognizing both verbal and nonverbal auditory stimuli. Cortical deafness is a rare syndrome that arises from a bilateral damage to the auditory cortex.

Strokes that interrupt all of the projection fibers from the medial geniculate nucleus to the various auditory cortical regions also cause deafness (Y. Tanaka et al., 1991). Patients who suffer from stroke-induced deafness still show various acoustic reflexes mediated by the brainstem—such as bodily responses to environmental sounds—although they deny hearing the sounds to which they are reacting. In contrast, patients with bilateral destruction of only the *primary* auditory cortex often have less-severe hearing loss, presumably because other auditory cortical regions contribute to hearing, as discussed earlier.

Electrical stimulation of the auditory pathway can alleviate deafness

As described already, many cases of sensorineural hearing loss involve damaged hair cells. Although the hair cells may be completely destroyed, the electrical excitability of the auditory nerve often remains unchanged. So one practical approach for circumventing deafness due to hair cell loss involves directly stimulating the auditory nerve with electrical currents (Loeb, 1990; J. M. Miller and Spelman, 1990). Progress in the development of **cochlear implants** that deliver such electrical stimulation has been rapid (**Figure 9.14**). Although some advocates of deaf culture oppose the use of such prostheses (Crouch, 1997), studies confirm an increase in speech perception with continued use of cochlear implants (Skinner et al., 1997).

Cochlear implants can provide only a limited range of frequencies and loudness, but the auditory information that they deliver can nonetheless greatly facilitate acoustically mediated behaviors. For example, this treatment makes it possible to distinguish voiced and unvoiced speech sounds (e.g., "v" and "f"), which cannot be distinguished in lip-reading. When a cochlear implant is turned on, functional imaging shows that the auditory cortex is activated (J. Ito et al., 1993; Klinke et al., 1999), and tonotopic organization of the activation is evident (Lazeyras et al., 2002), indicating that this region is processing the information. Furthermore, the earlier the implants are provided, the better the eventual performance is (Rauschecker, 1999). The success of these implants is due mainly to the cleverness of the brain, not the implant.

A new generation of implantable aids, called **auditory brainstem implants** (**ABIs**), produce auditory sensations by directly stimulating the cochlear nuclei of the brainstem. By bypassing the ear altogether, ABI devices offer hope of hearing restoration even for those who lack a functional auditory nerve (Rauschecker and Shannon, 2002). Preliminary work suggests that direct stimulation of the auditory midbrain (the inferior colliculi) may provide an additional option for restoring hearing in such cases (Lenarz et al., 2006).

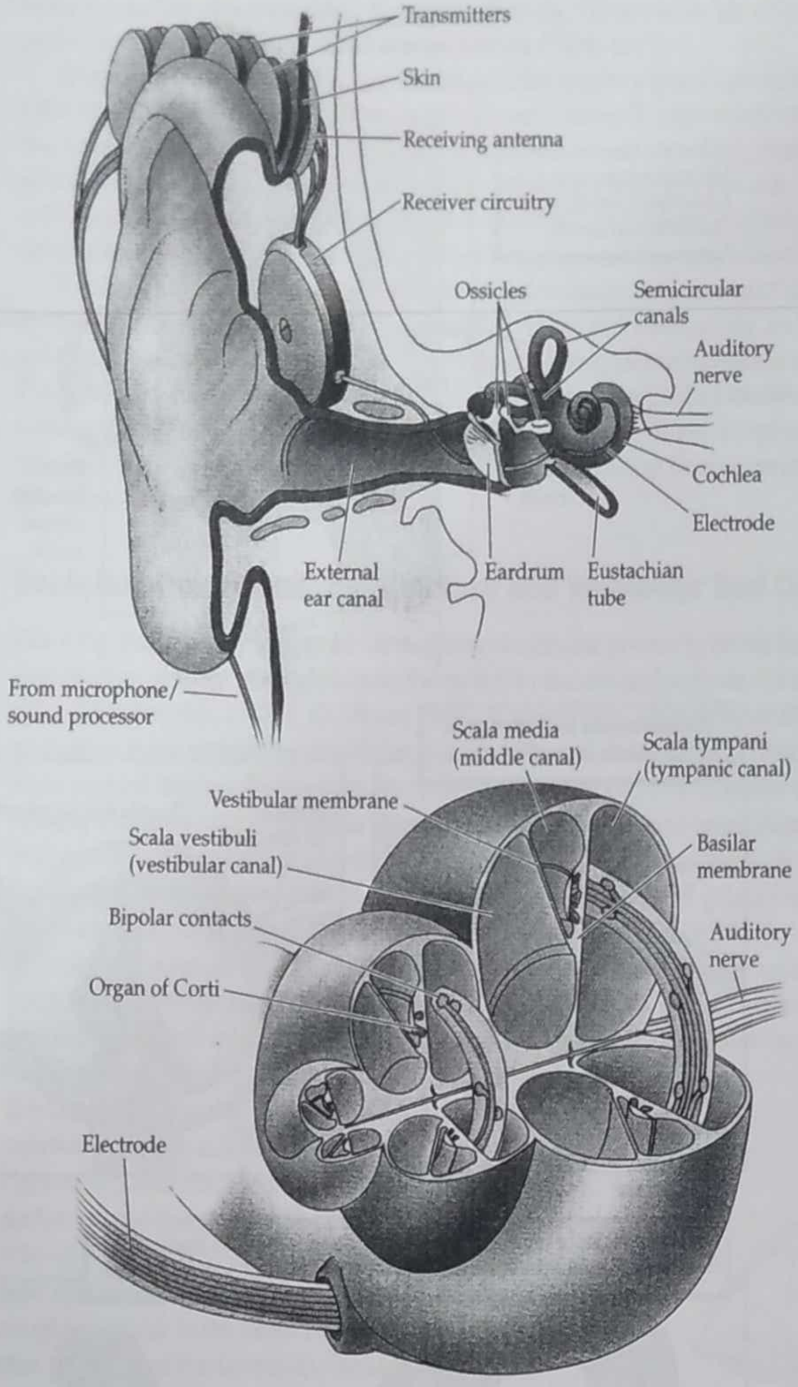
central deafness A hearing impairment that is related to lesions in auditory pathways or centers, including sites in the brainstem, thalamus, or cortex.

word deafness The specific inability to hear words, although other sounds can be detected.

cortical deafness A hearing impairment that is caused by a fault or defect in the cortex.

cochlear implant An electromechanical device that detects sounds and selectively stimulates nerves in different regions of the cochlea via surgically implanted electrodes.

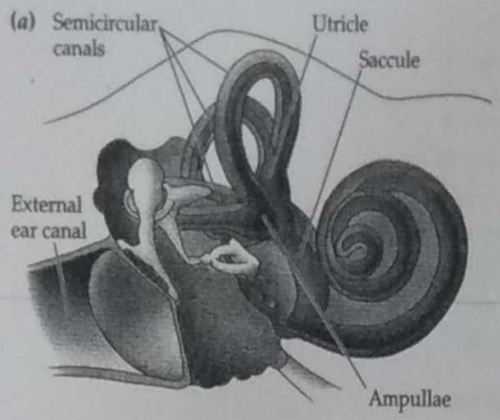
auditory brainstem implant (ABI) A type of auditory prosthesis in which implanted microphones directly stimulate the auditory nuclei of the brainstem rather than the cochlea.

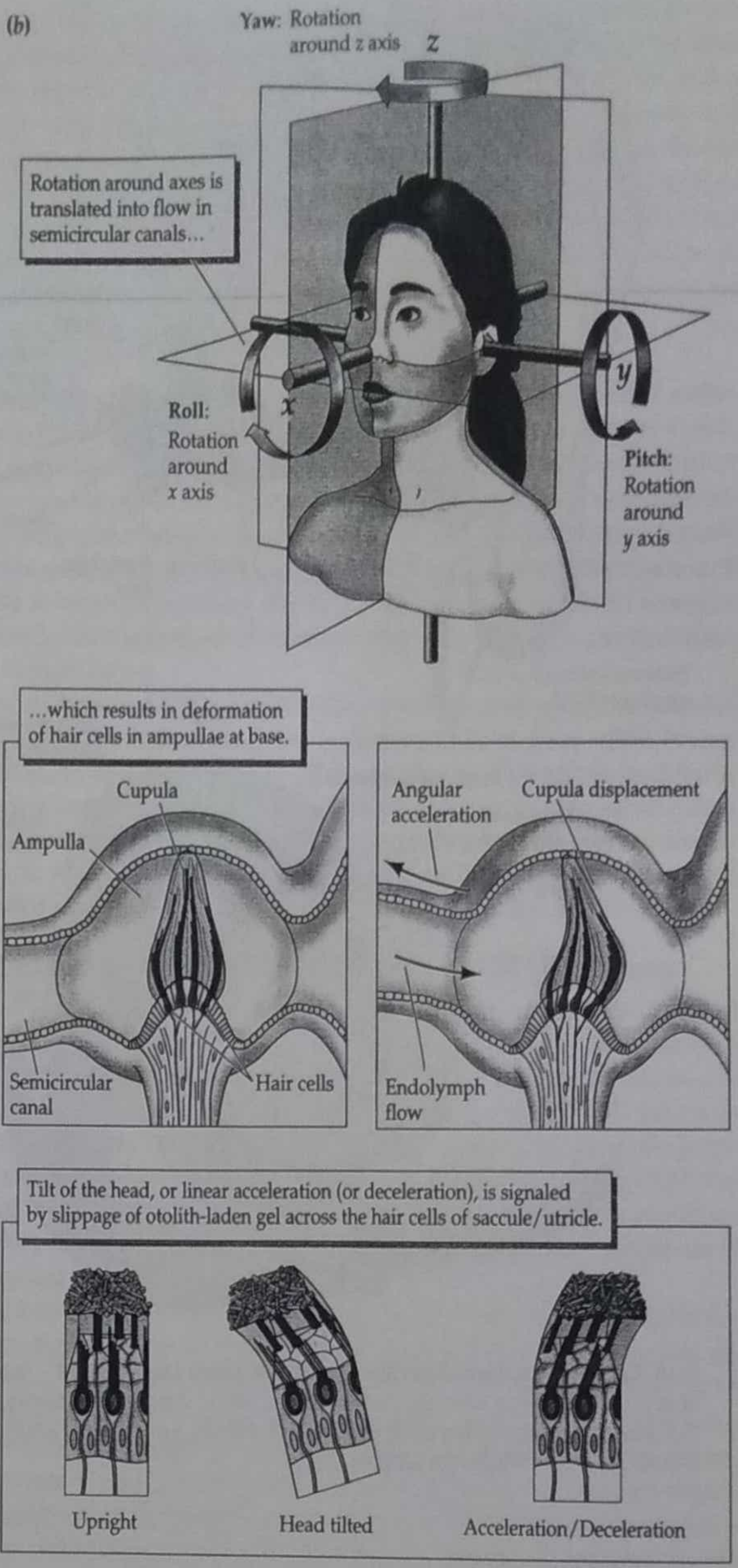

Transmitters
Skin
Receiving antenna
Receiver circuitry
Ossicles
Semicircular canals
Auditory nerve
Cochlea
Electrode
External ear canal
Eardrum
Eustachian tube
From microphone/ sound processor
Scala media (middle canal)
Scala tympani (tympanic canal)
Vestibular membrane
Scala vestibuli (vestibular canal)
Basilar membrane
Bipolar contacts
Auditory nerve
Organ of Corti
Electrode

9.14 Cochlear Implants Provide Hearing in Some Deaf People A microphone detects sound and directs the cochlear implant circuitry to stimulate the auditory nerve. Although this apparatus provides only a crude simulation of ordinary auditory nerve activity, the brain can learn to use the information to decipher speech.

Vestibular Perception

The vestibular system provides information about the force of gravity on the body and the acceleration of the head. When you go up in an elevator, you feel the acceleration clearly. When you turn your head or ride in a car going around a tight curve, you feel the change of direction. If you are not used to these kinds of stimulation, sensitivity to motion can make you queasy. The receptors of the vestibular system inform the brain about mechanical forces that act on the body.


(a) Semicircular canals
Utricle
Saccule
External ear canal
Ampullae


(b)
Yaw: Rotation around z axis
Z
Rotation around axes is translated into flow in semicircular canals...
x
y
Roll: Rotation around x axis
Pitch: Rotation around y axis
...which results in deformation of hair cells in ampullae at base.
Cupula
Ampulla
Semicircular canal
Hair cells
Angular acceleration
Cupula displacement
Endolymph flow
Tilt of the head, or linear acceleration (or deceleration), is signaled by slippage of otolith-laden gel across the hair cells of saccule/utricle.
Upright
Head tilted
Acceleration/Deceleration

9.15 Structures of the Vestibular System (a) The vestibular apparatus is located in the temporal bone, continuous with the cochlea. The semicircular canals are connected through ampullae to the utricle, which connects to the saccule. (b) The semicircular canals detect rotation in three planes; hair cells in the ampullae detect flow of endolymph in the canals when the head is rotated. The utricle and saccule detect linear acceleration and static position, aided by tiny crystals, called *otoliths*, that overlie the hair cells in these structures and maximize the deflection of hair cells in response to movement.

The Receptor Mechanisms for the Vestibular System Are in the Inner Ear

semicircular canal One of the three fluid-filled tubes in the inner ear that are part of the vestibular system. Each of the tubes, which are at right angles to each other, detects angular acceleration.

The receptors of the vestibular system lie within the inner ear next to the cochlea. (The term *vestibular* comes from the Latin *vestibulum*, "entrance hall," and reflects the fact that the system lies in hollow spaces in the temporal bone.) In mammals, one portion of the vestibular system consists of three **semicircular canals**, fluid-filled tubes that are each oriented in a different plane (**Figure 9.15a**). The three canals are connected at their ends to a saclike structure called the **utricle** (literally, "little uterus"). Lying below the utricle is another small fluid-filled sac, the **saccule** ("little sac").

Receptors in these structures, just like those of the auditory system, are groups of hair cells whose bending leads to the excitation of nerve fibers. In each semicircular canal, the hair cells are in an enlarged region, the **ampulla** (plural *ampullae*), that lies at the junction between each canal and the utricle (**Figure 9.15*b***). Here the cilia of the hair cells are embedded in a gelatinous mass. The orientation of the hairs is quite precise and determines the kind of mechanical force to which they are especially sensitive.

The three semicircular canals are at right angles to each other, so one or another detects rotational acceleration in any direction. The receptors in the saccule and utricle respond to vertical and horizontal linear forces, and thus signal static position as well (see Figure 9.15*b*). Small bony crystals on the gelatinous membrane, called **otoliths** (from the Greek *ot-*, "ear," and *lithos*, "stone"), increase the sensitivity of these receptors to movement. At the base of the hair cells in these receptors are nerve fibers connected much like those that connect auditory hair cells.

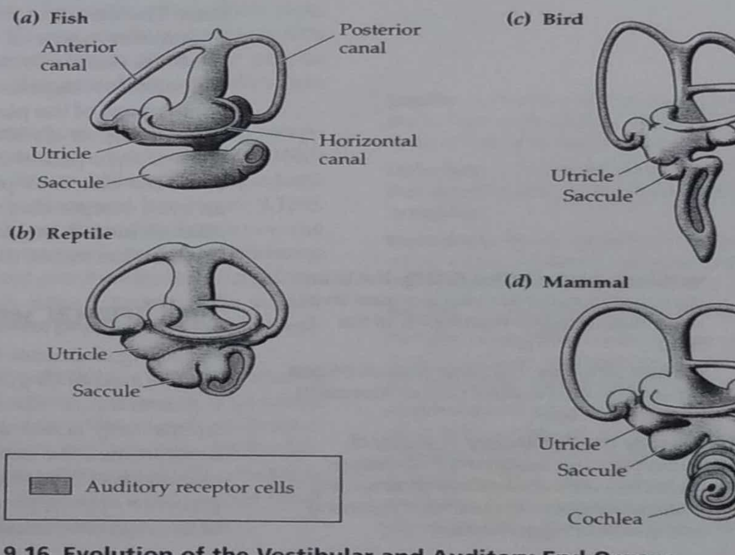
Evolution Has Shaped the Auditory and Vestibular End Organs

The long evolutionary history of the auditory–vestibular system is better known than that of other sensory systems because the receptors are encased in bone, which can fossilize (Van Bergeijk, 1967; E. G. Wever, 1974). It is generally accepted that the auditory end organ evolved from the vestibular system, although the ossicles probably evolved from parts of the jaw. Before that, the vestibular system evolved from the **lateral-line system**, a sensory system found in many kinds of fishes and some amphibians. The lateral-line system consists of an array of receptors along the side of the body. Tiny hairs that emerge from sensory cells in the skin are embedded in small gelatinous columns called **cupulae** (singular *cupula*), like those in mammals (see Figure 9.15*b*).

In aquatic animals with lateral-line systems, movements of water in relation to the body surface stimulate these receptors so that the animal can detect currents of water and movements of other animals, prey, or predators. It is speculated that the first semicircular canals developed from a stretch of lateral-line canal that migrated inside the body. This development gave the animal a sensor for turns to the right or left, and this receptor, being away from the surface of the body, was free of effects of stimulation of the skin. Sensitivity to change of direction was optimized when the canal developed into a roughly circular form. From the vestibular system that arose out of the lateral-line system evolved the auditory system (**Figure 9.16**).

Nerve Fibers from the Vestibular Portion of the Vestibulocochlear Nerve (VIII) Synapse in the Brainstem

The structural arrangements of brain pathways dealing with the vestibular system reflect its importance to motor control and posture. Nerve fibers from the vestibular receptors enter lower levels of the brainstem and synapse in the **vestibular nuclei**. Some of the fibers bypass this structure and go directly to the cerebellum, contributing to its motor functions. The outputs of the vestibular nuclei are complex, as is appropriate, considering their influ-



9.16 Evolution of the Vestibular and Auditory End Organs

utricle A small, fluid-filled sac in the vestibular system above the saccule that responds to static positions of the head.

saccule A small, fluid-filled sac under the utricle in the vestibular system that responds to static positions of the head.

ampulla An enlarged region of each semicircular canal that contains the receptor cells (hair cells) of the vestibular system.

otolith A small bony crystal on the gelatinous membrane in the vestibular system.

lateral-line system A sensory system, found in many kinds of fishes and some amphibians, that informs the animal of water motion in relation to the body surface.

cupula A small gelatinous column that forms part of the lateral-line system of aquatic animals and also occurs within the vestibular system of mammals.

vestibular nuclei Brainstem nuclei that receive information from the vestibular organs through cranial nerve VIII (the vestibulocochlear nerve).

ences on the motor system. These outputs go to the motor nuclei of the eye muscles, the thalamus, and the cerebral cortex, among others.

One of the many important functions of the vestibular system is the precise control of eye movements. Try moving your head around while staring at a particular spot on the wall. It seems almost effortless to maintain your gaze on the fixation point, but in reality it is a very complex processing problem; the six muscles that control the movement of each eye must rapidly and precisely counter the movements of the head as they occur. This function is called the **vestibulo-ocular reflex** (**VOR**), involving a high-speed network within the brainstem that draws on vestibular information about head rotations to move the eyes in compensation. That the VOR functions accurately even when the eyes are closed is evidence that vestibular inputs—rather than visual ones—control the accuracy of gaze as we move through the world.

Some Forms of Vestibular Excitation Produce Motion Sickness

There is one aspect of vestibular activation that many of us would gladly do without. Certain types of body acceleration—as when riding in a boat, car, plane, or roller coaster—can produce the misery of **motion sickness**. *Caloric stimulation*—the pouring of warm or cold water into one ear canal—produces the same effect by initiating movements of inner-ear fluids that simulate body movements. Motion sickness is caused especially by movements of the body that an individual cannot control. For example, passengers in a car are more likely to suffer from motion sickness than is the driver.

Why do we experience motion sickness? Michel Treisman (1977) hypothesized that the sensory conflict of some conditions of motion sets off responses that evolved to rid the body of swallowed poison. According to this hypothesis, discrepancies in sensory information normally signal danger and cause dizziness and vomiting to get rid of potentially toxic food. Such a response has obvious significance for preservation of life, although it is not helpful as a response to movements of vehicles.

One major theory of motion sickness—**sensory conflict theory**—argues that we feel bad when we receive contradictory sensory messages, especially a discrepancy between vestibular and visual information. When an airplane bounces around in turbulence, for instance, the vestibular system signals that various accelerations are occurring, but as far as the visual system is concerned, nothing is happening; the plane's interior is a constant. The resulting disorientation is distressing for passengers (A. J. Benson, 1990).

A different type of vestibular disorientation can strike airplane pilots. Note from Figure 9.15*b* that linear acceleration and an upward head tilt produce the same stimulation of the otolith organs: the saccule and utricle. So in conditions of very low visibility, an acceleration of the plane may be misinterpreted as a climb (an upward tilt of the plane) (Macneilage et al., 2006). This *false-climb illusion* can be very compelling, leading pilots to force their planes into a dive because they mistakenly believe they are climbing. Because the dive itself produces further acceleration, heightening the illusion of climbing, an even steeper dive may be adopted, with tragic consequences. Fortunately, pilots of modern aircraft making landings in low-visibility conditions learn to rely on a variety of instruments rather than on their vestibular systems.

The Chemical Senses: Taste and Smell

Detecting chemicals in the environment is vital for the survival of organisms throughout the animal kingdom. The sense of taste provides an immediate assessment of foods (Lindemann, 1995): sweet indicates high-calorie foods; savory tastes signal a protein source; salty and sour relate to important aspects of homeostasis; bitter warns of toxic constituents. The sense of smell is critical for appreciating the rich and complex flavors of individual foods but has additional important functions as well, such as signaling the presence of prey, predators, or potential mates. This section will explore the many roles of the chemical senses—taste and smell—in guiding behavior.

vestibulo-ocular reflex (VOR) The brainstem mechanism that maintains gaze on a visual object despite movements of the head.

motion sickness The experience of nausea brought on by unnatural passive movement, as in a car or boat.

sensory conflict theory A theory of motion sickness suggesting that discrepancies between vestibular information and visual information simulate food poisoning and therefore trigger nausea.

Chemicals in Tastants Elicit Taste Sensations

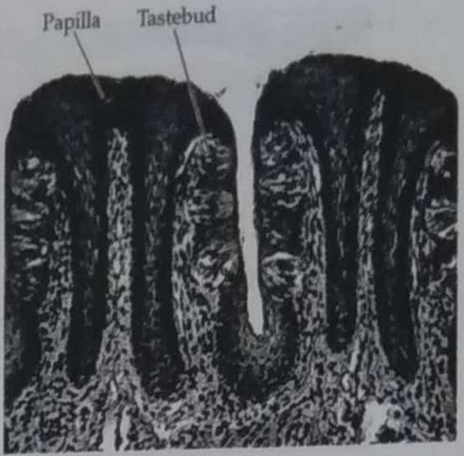
We'll start our review of the chemical senses with taste, which is somewhat simpler than smell and in some ways has been more thoroughly investigated.

Humans detect five basic tastes

Most people derive great pleasure from eating delicious food, and because we recognize many substances by their distinct flavor, we tend to think that we can discriminate many tastes. In reality, though, humans detect only five basic tastes: salty, sour, sweet, bitter, and umami. (*Umami*, Japanese for "delicious taste," is the savory, meaty taste that is characteristic of broth).

The sensations uniquely aroused by an apple, a steak, or an olive are *flavors* rather than simple tastes; they involve smell as well as taste. Block your nose, and a potato tastes the same as an apple. Our ability to respond to many odors—it is estimated that humans can detect more than 10,000 different odors and can discriminate as many as 5000 (Ressler et al., 1994)—is what produces the complex array of flavors that we normally think of as tastes. Ordinarily, smell and taste work together, such that detecting certain tastes makes it easier to detect certain odors (P. Dalton et al., 2000). Although the taste system is very similar across different species of mammals, there is some variability; for example, cats are not sensitive to sweet.

The ability to taste many substances is already well developed in humans at birth. Even premature infants show characteristic responses to different tastes, sucking in response to a sweet substance but trying to spit out a bitter substance. Newborns seem to be relatively insensitive to salty tastes, but a preference for mildly salty substances develops in the first few months. This preference does not seem to be related to experience with salty tastes; rather it probably indicates maturation of the mechanisms of salt perception (Beauchamp et al., 1994).



9.17 A Cross Section of the Tongue

Tastes excite specialized receptor cells on the tongue

In mammals, most taste receptor cells are located on small projections from the surface of the tongue; these little bumps are called **papillae** (singular *papilla*; Latin for "nipples") (**Figure 9.17**). Each papilla holds one or more **taste buds**, and each taste bud consists of a cluster of 50 to 150 taste receptor cells (**Figure 9.18*a***). At the surface end of the taste bud is an opening called the **taste pore** (**Figure 9.18*b***). The taste cells extend fine cilia into the taste pore, which come into contact with **tastants** (substances that can be tasted). As we'll discuss a little later, each taste receptor cell appears to specifically sense just one of the five basic tastes.

Not all of the sensory cells in taste buds signal taste sensations; some are pain receptors responding to stimuli such as "hot" red pepper, and others are touch receptors. With a life span of only 10 to 14 days, taste cells are constantly being replaced. A single taste bud has receptor cells that are at many different stages of development (see Figure 9.18*b*).

There are three kinds of taste papillae; **Figure 9.18*c*** shows their distribution on the tongue. The most numerous are **fungiform papillae**, which resemble button mushrooms in shape (*fungus* is Latin for "mushroom"). The tongue contains hundreds of fungiform papillae, but the numbers vary greatly among individuals. A fungiform papilla usually contains only a single taste bud. Each of the few **circumvallate papillae** and **foliate papillae** contains several taste buds.

Many books show a map of the tongue indicating that each taste is perceived mainly in one region (sweet at the tip of the tongue, bitter at the back, and so on), but Linda Bartoshuk (1993), a specialist in taste psychophysics, states that this map is erroneous: "The [usual] tongue map has become an enduring scientific myth" (p. 253). All five basic tastes can be perceived *anywhere* on the tongue where there are taste receptors (Collings, 1974; Yanagisawa et al., 1992; Chandrashekar, 2006). The areas do not differ greatly in the strength of taste sensations that they mediate (see Figure 9.18*c*).

papilla A small bump that projects from the surface of the tongue. Papillae contain most of the taste receptor cells.

taste bud A cluster of 50 to 150 cells that detects tastes. Taste buds are found in papillae.

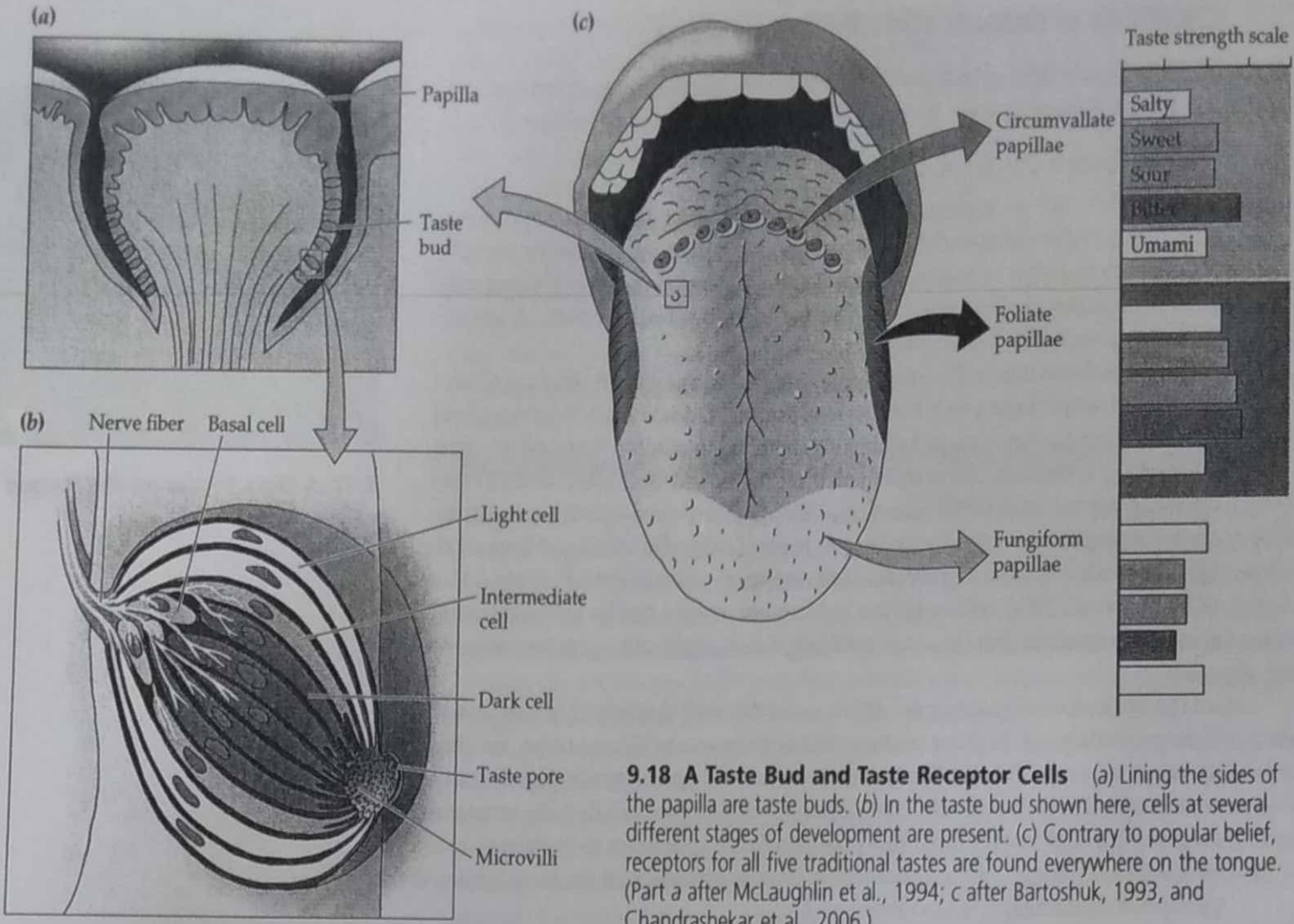
taste pore The small aperture through which tastant molecules are able to access the sensory receptors of the taste bud.

tastant A substance that can be tasted.

fungiform papillae One of three types of small structures on the tongue, located in the front, that contain taste receptors.

circumvallate papillae One of three types of small structures on the tongue, located in the back, that contain taste receptors.

foliate papillae One of three types of small structures on the tongue, located along the sides, that contain taste receptors.



9.18 A Taste Bud and Taste Receptor Cells (a) Lining the sides of the papilla are taste buds. (b) In the taste bud shown here, cells at several different stages of development are present. (c) Contrary to popular belief, receptors for all five traditional tastes are found everywhere on the tongue. (Part a after McLaughlin et al., 1994; c after Bartoshuk, 1993, and Chandrashekar et al., 2006.)

Different cellular processes transduce the basic tastes

The tastes salty and sour are evoked when taste cells are stimulated by simple ions acting on ion channels in the membranes of the taste cells. Sweet and bitter tastes are perceived by specialized receptor molecules and communicated by second messengers. At least two types of receptors may be involved in the perception of umami.

SALTY Sodium ions (Na^+) are transported across the membranes of taste cells by sodium ion channels. Blocking these channels with a drug greatly reduces the salty taste of sodium chloride in both humans and rats; facilitating the passage of Na^+ across the membrane with another drug intensifies salty tastes (Schiffman et al., 1986). The entry of sodium ions partially depolarizes the taste cells and causes them to release neurotransmitters that stimulate the afferent neurons that relay the information to the brain. Blockade of sodium channels does not completely eradicate salt taste, however. A second salt receptor, a variant of a receptor called **TRPV1** (**transient receptor potential vanilloid type 1**) provides this additional sensitivity to Na^+, as well as other cations from salts (such as K^+ and Ca^{2+}) (Lyall et al., 2004; Treesukosol et al., 2007). Transient receptor potential (TRP) proteins form a large family of receptors that are sensitive to external stimuli of many kinds.

SOUR An acid tastes sour, whether it is a simple inorganic compound, such as hydrogen chloride, or a more complex organic compound, such as lactic acid. The property that all acids share is that they release hydrogen ions (H^+). A number of mechanisms have been proposed for sour detection, especially acid-sensing ion channels. For example, one type of potassium channel is blocked by H^+, preventing the release of potas-

transient receptor potential vanilloid type 1 (TRPV1) A receptor that binds capsaicin to transmit the burning sensation from chili peppers. TRPV1 may be the receptor for detecting sudden increases in temperature.

sium ions (K^+) from taste cells and causing depolarization and neurotransmitter release. Although the exact mechanisms of sour detection are not completely understood, sour-specific taste cells all appear to need one particular type of ion channel (called PKD2L1) in order to function (A. L. Huang et al., 2006). This channel is probably part of the basic sour taste receptor protein.

SWEET The molecular mechanisms in the transduction of sweet, bitter, and umami tastes are more complex than those responsible for salty and sour tastes. Sweet, bitter, and umami tastants appear to stimulate specialized receptor molecules on membranes of the taste cells, causing a cascade of internal cellular events involving G proteins and second messengers.

Investigators have identified two families of G protein–coupled taste receptors, designated **T1R** and **T2R**, that are expressed by some taste cells. These receptors function much like the slow metabotropic receptors that we considered in Chapter 3, although they may employ a unique G protein alpha subunit, called *gustducin*, that has been isolated in taste cells (McLaughlin et al., 1994).

Two members of the T1R family—T1R2 and T1R3—combine (*heterodimerize*) to function as a sweet receptor in taste cells (G. Nelson et al., 2001), recognizing a wide array of sweet-tasting substances. Mice lacking T1R2 or T1R3—and particularly knockout mice that lack both components—are rendered insensitive to sweet tastes (Zhao et al., 2003). Dozens of substances taste sweet, so how can a single receptor be sensitive to sweet molecules that are as different as, for example, sugar, aspartame, and saccharin? Different sweet tastants appear to interact with different recognition sites within the T1R2+T1R3 receptor complex (Cui et al., 2006).

If you've spent any time around cats, you may be aware that they couldn't care less about sweets. It turns out that all cats, from house cats to leopards, share a mutation in the gene that encodes T1R2; their sweet receptors don't work (X. Li et al., 2005).

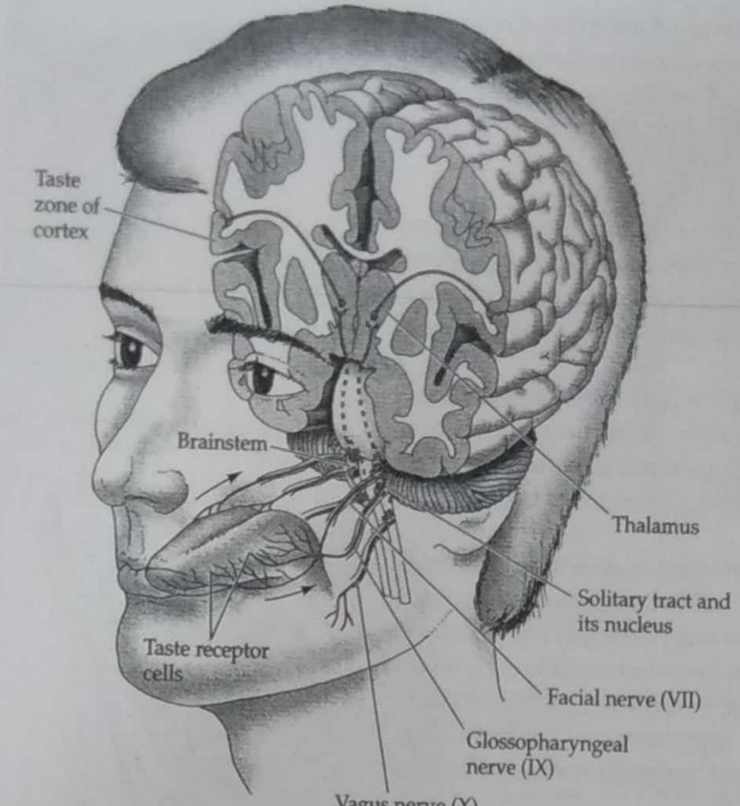
BITTER Bitter sensations are evoked by many different tastants. The association of bitter tastes with many toxic substances—such as nicotine, caffeine, strychnine, and morphine—provided strong evolutionary pressure to develop a high sensitivity to bitterness. The fact that different bitter substances can be discriminated—as determined by psychophysical work with human tasters (McBurney et al., 1972) and with animal subjects (Lush, 1989)—suggested that there is more than one receptor for bitterness.

Members of the T2R family of G protein–coupled receptors appear to be bitter receptors (E. Adler et al., 2000; Chandrashekar et al., 2000). The T2R family has about 30 members, and this large number may reflect the wide variety of bitter substances encountered in the environment, as well as the adaptive importance of being able to detect and avoid them. Interestingly, each bitter-sensing taste cell produces most or all of the different types of T2R bitter receptors (E. Adler, et al., 2000). This means that these taste cells serve as broadly tuned bitter sensors: the cells are sensitive to any of a wide variety of bitter substances, but not very good at encoding qualitative distinctions *between* different types of bitterness. This makes sense from an evolutionary point of view: if bitterness signals toxicity, then being able to sensitively detect *any* bitterness is far more important than being able to evaluate the qualities of specific bitter tastes. The observation that rats and mice have only limited abilities to distinguish between different kinds of bitter substances (Brasser et al., 2005) buttresses this idea.

About 25% of people in the United States cannot taste the chemical phenylthiocarbamide (PTC) and the related compound 6-*n*-propylthiouracil (PROP), even though they can taste other bitter substances. Family studies indicate that tasters and nontasters are genetically different. Furthermore, some people, referred to as *supertasters*, exhibit heightened sensitivity to some bitter tastes, suggesting that they are genetically different as well (Bartoshuk and Beauchamp, 1994). In fact, supertasters also enjoy stronger sweet sensations from some substances. Nontasters of PROP have the fewest taste buds (averaging 96 per square centimeter) on the tongue tip, medium tasters have an intermediate number (184), and supertasters have the most (425) (Reedy et al., 1993).

T1R A family of taste receptor proteins that, when particular members heterodimerize, form taste receptors for sweet flavors and umami flavors.

T2R A family of bitter taste receptors.



9.19 Anatomy and Main Pathways of the Human Gustatory System

UMAMI The fifth basic taste, **umami**, is described as a meaty, savory flavor. For most of the twentieth century, researchers argued about whether a distinct umami taste existed, but we now know that at least two types of receptors appear to be specialized to respond to exactly this sort of tastant. One of these, a variant of the metabotropic glutamate receptor, is expressed in certain taste buds (Chaudhari et al., 2000; Maruyama et al., 2006) and likely responds to the amino acid glutamate. Monosodium glutamate (MSG), which is used widely in cooking, undoubtedly stimulates this taste receptor.

Foods rich in protein will, of course, also be rich in amino acids, and this seems like useful information for an animal to detect. It turns out that a second probable umami receptor is a heterodimer of T1R1 and T1R3 receptors. Despite the similarity to the T1R2+T1R3 sweet receptor described already, the T1R1+T1R3 receptor selectively responds to most of the 20 standard amino acids that might be encountered in the diet (G. Nelson et al., 2002).

In mice lacking the gene that encodes the T1R3 receptor, sensitivity to sweet and umami tastants is greatly reduced but not abolished (Damak et al., 2003), implying that there must be additional receptor systems for these tastes that are T1R3-independent. It also suggests that the especially attractive tastes—sweet and umami—may have shared evolutionary origins. The hunt for other types of taste receptors continues.

Taste information is transmitted to several parts of the brain

The **gustatory system** (from the Latin *gustare*, "to taste") extends from the taste receptor cells through brainstem nuclei and the thalamus to the cerebral cortex (**Figure 9.19**). Each taste cell transmits information to several afferent fibers, and each afferent fiber receives information from several taste cells. The afferent fibers run along three different cranial nerves—the facial (VII), glossopharyngeal (IX), and vagus (X) nerves (see Figure 2.9). The gustatory fibers in each of these nerves run to the brainstem. Here they synapse with second-order gustatory fibers that run to the ventral posterior medial nucleus of the thalamus. After another synapse, third-order gustatory fibers run to the cortical taste areas in the somatosensory cortex.

For several decades it has been thought that individual taste cells express receptors for more than one of the five kinds of tastes, and that the brain extrapolates taste information from **pattern coding**, the relative activity across ensembles of axons from different taste receptor cells. However, selectively destroying taste cells that express receptors for just one of the five tastes tends to completely eradicate sensitivity to that one taste while leaving the other four tastes unaffected (A. L. Huang et al., 2006). These effects suggest that taste is actually a simple system of **labeled lines**, in which there are five classes of taste receptor cell—one type for each taste (plus the sensors for heat, pain, and so on that we discussed earlier). Taste perception is thus determined by the specific axons that are active rather than by the pattern of activity across groups (Chandrashekar et al., 2006).

Chemicals in the Air Elicit Odor Sensations

Many aspects of an animal's world are determined by chemicals carried in the air. Olfactory sensitivity varies widely across species of mammals: cats and mice, dogs and rabbits—all have a sharper sense of smell than humans. In the 1980s, a large survey of olfaction revealed widespread partial **anosmia** (odor blindness) among humans, with men exhibiting slightly worse olfaction than women (Gilbert and Wysocki, 1987). Dolphins don't have olfactory receptors at all (Freitag et al., 1998). These differences evolved be-

umami One of the five basic tastes (along with salty, sour, sweet, and bitter), probably mediated by amino acids in foods.

gustatory system The taste system.

pattern coding Coding of information in sensory systems based on the temporal pattern of action potentials.

labeled lines The concept that each nerve input to the brain reports only a particular type of information.

anosmia The inability to smell.

cause of variability in the importance of smell for survival and reproduction. Nevertheless, different species of mammals, including humans, accomplish olfaction in much the same way, as we will describe next.

The sense of smell starts with receptor neurons in the nose

In humans, a sheet of cells called the **olfactory epithelium** (**Figure 9.20**) lines the dorsal portion of the nasal cavities and adjacent regions, including the septum that separates the left and right nasal cavities. Within the olfactory epithelium of the nasal cavity are three types of cells: receptor neurons, supporting cells, and basal cells. At least 6 million olfactory receptor neurons are found in the 2-cm^2 area of human olfactory epithelium. In many other mammals this number is an order of magnitude greater; for example, rabbits have about 40 million receptor neurons in the olfactory epithelium.

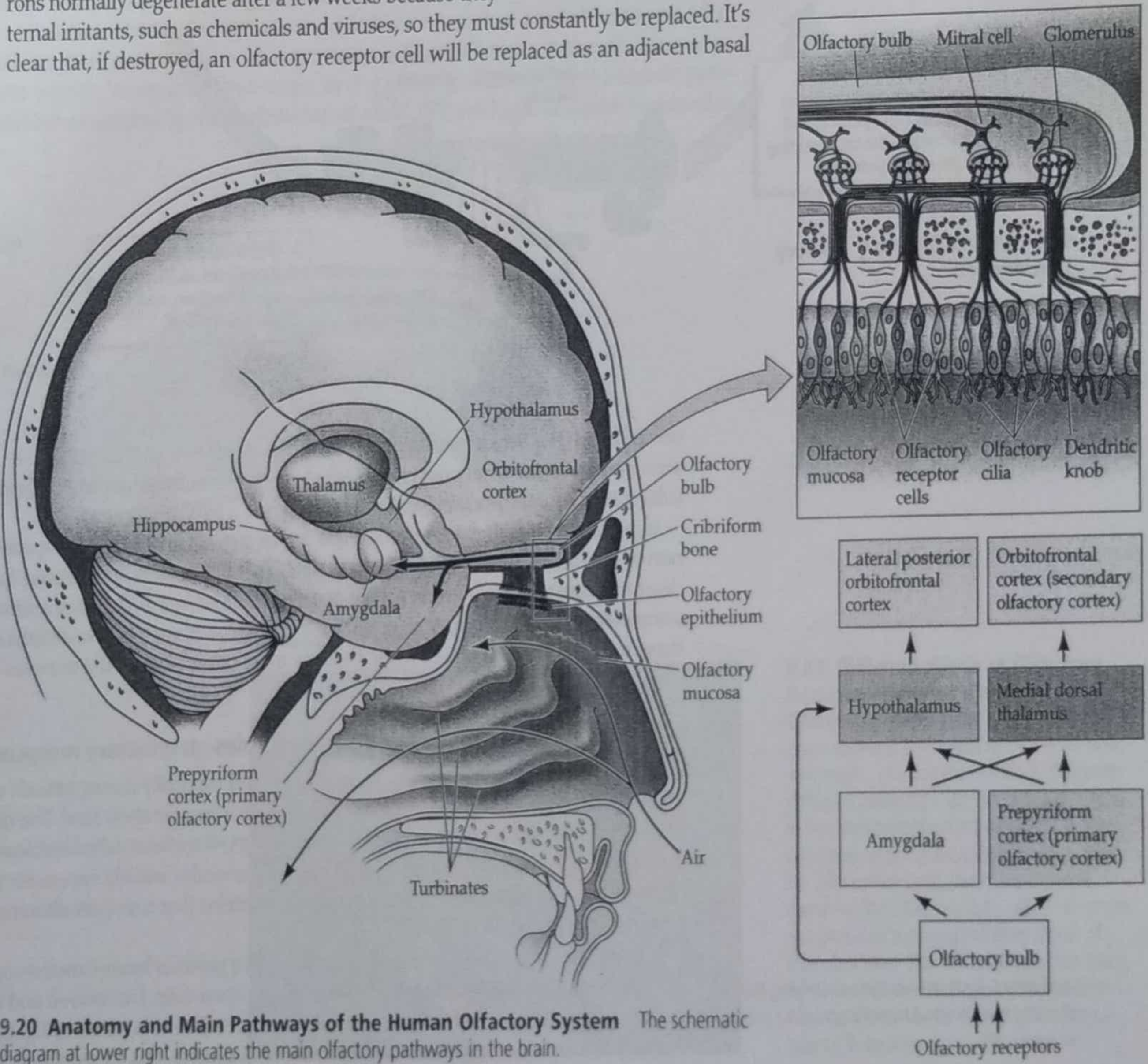
Each receptor cell has a long, slender apical dendrite that extends to the outermost layer of the epithelium, the mucosal surface. There, numerous **cilia** (singular *cilium*) emerge from the **dendritic knob** and extend along the mucosal surface. At the opposite end of each bipolar olfactory receptor cell, a fine, unmyelinated axon, which is among the smallest-diameter axons in the nervous system, runs to the olfactory bulb (which we will discuss shortly).

In contrast with many other receptor neurons in the body, olfactory receptor neurons can be replaced in adulthood (Costanzo, 1991). One theory is that these receptor neurons normally degenerate after a few weeks because they are in direct contact with external irritants, such as chemicals and viruses, so they must constantly be replaced. It's clear that, if destroyed, an olfactory receptor cell will be replaced as an adjacent basal

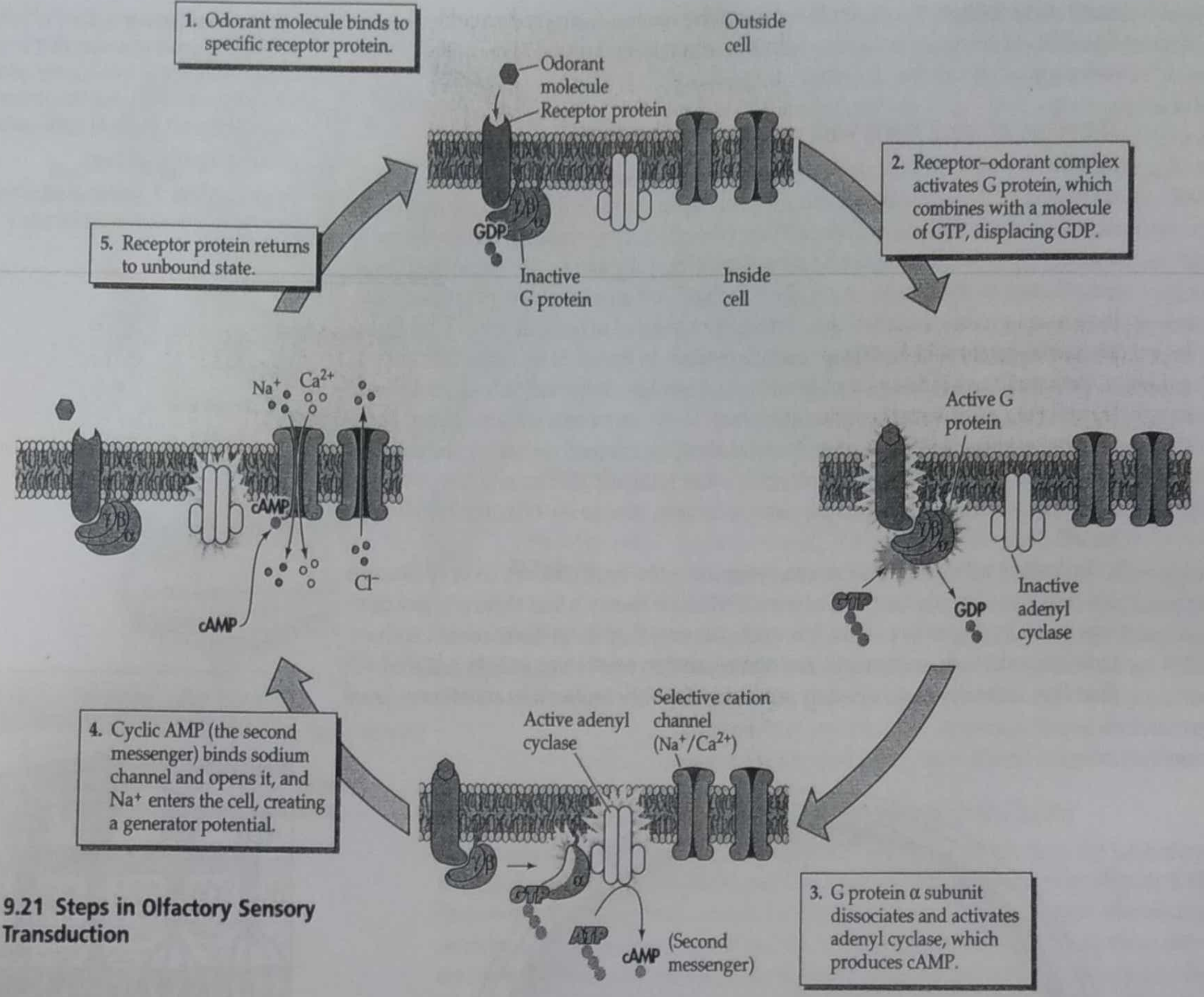
olfactory epithelium A sheet of cells, including olfactory receptors, that lines the dorsal portion of the nasal cavities and adjacent regions, including the septum that separates the left and right nasal cavities.

cilium A hairlike extension.

dendritic knob A portion of olfactory receptor cells present in the olfactory epithelium.


Olfactory bulb
Mitral cell
Glomerulus
Olfactory mucosa
Olfactory receptor cells
Olfactory cilia
Dendritic knob
Hypothalamus
Thalamus
Orbitofrontal cortex
Hippocampus
Amygdala
Olfactory bulb
Cribriform bone
Olfactory epithelium
Olfactory mucosa
Prepyriform cortex (primary olfactory cortex)
Turbinates
Air
Lateral posterior orbitofrontal cortex
Orbitofrontal cortex (secondary olfactory cortex)
Hypothalamus
Medial dorsal thalamus
Amygdala
Prepyriform cortex (primary olfactory cortex)
Olfactory bulb
Olfactory receptors

9.20 Anatomy and Main Pathways of the Human Olfactory System The schematic diagram at lower right indicates the main olfactory pathways in the brain.


1. Odorant molecule binds to specific receptor protein.
Outside cell
Odorant molecule
Receptor protein
GDP
Inactive G protein
Inside cell
2. Receptor–odorant complex activates G protein, which combines with a molecule of GTP, displacing GDP.
Active G protein
GTP
GDP
Inactive adenyl cyclase
3. G protein α subunit dissociates and activates adenyl cyclase, which produces cAMP.
Active adenyl cyclase
Selective cation channel (Na⁺/Ca²⁺)
GTP
ATP
cAMP
(Second messenger)
4. Cyclic AMP (the second messenger) binds sodium channel and opens it, and Na⁺ enters the cell, creating a generator potential.
Na⁺
Ca²⁺
cAMP
Cl⁻
cAMP
5. Receptor protein returns to unbound state.
β
γ
α

9.21 Steps in Olfactory Sensory Transduction

cell differentiates into a neuron and extends dendrites to the mucosal surface and an axon into the brain. What's not clear is whether receptor cells are *normally* "disposable," subject to constant turnover even in the absence of a particular trauma.

If the olfactory epithelium is damaged, it can be regenerated and will properly reconnect to the olfactory bulb. The functional capability of these new connections has been clearly demonstrated in both behavioral and electrophysiological studies of animals with completely regenerated olfactory epithelium. Investigators are trying to determine how these neurons can regenerate while those in most other parts of the nervous system cannot.

Odorants excite specialized receptor molecules on olfactory receptor cells

Odorants enter the nasal cavity during inhalation and especially during periods of sniffing; they also rise to the nasal cavity from the mouth when we chew food. The direction of airflow in the nose is determined by complex curved surfaces called **turbinates** that form the nasal cavity (see Figure 9.20). Airborne molecules initially encounter the fluids of the mucosal layer, which contain binding proteins that transport odorants to receptor surfaces (Farbman, 1994).

The odorant stimulus then interacts with receptor proteins located on the surface of the olfactory cilia and the dendritic knob of the receptor cells. Discovered and characterized by Linda Buck, Richard Axel, and collaborators (Buck and Axel, 1991), these receptor proteins are members of a superfamily of G protein–linked receptors. Interac-

turbinates Complex shapes underlying the olfactory mucosa that direct inspired air over receptor cells.

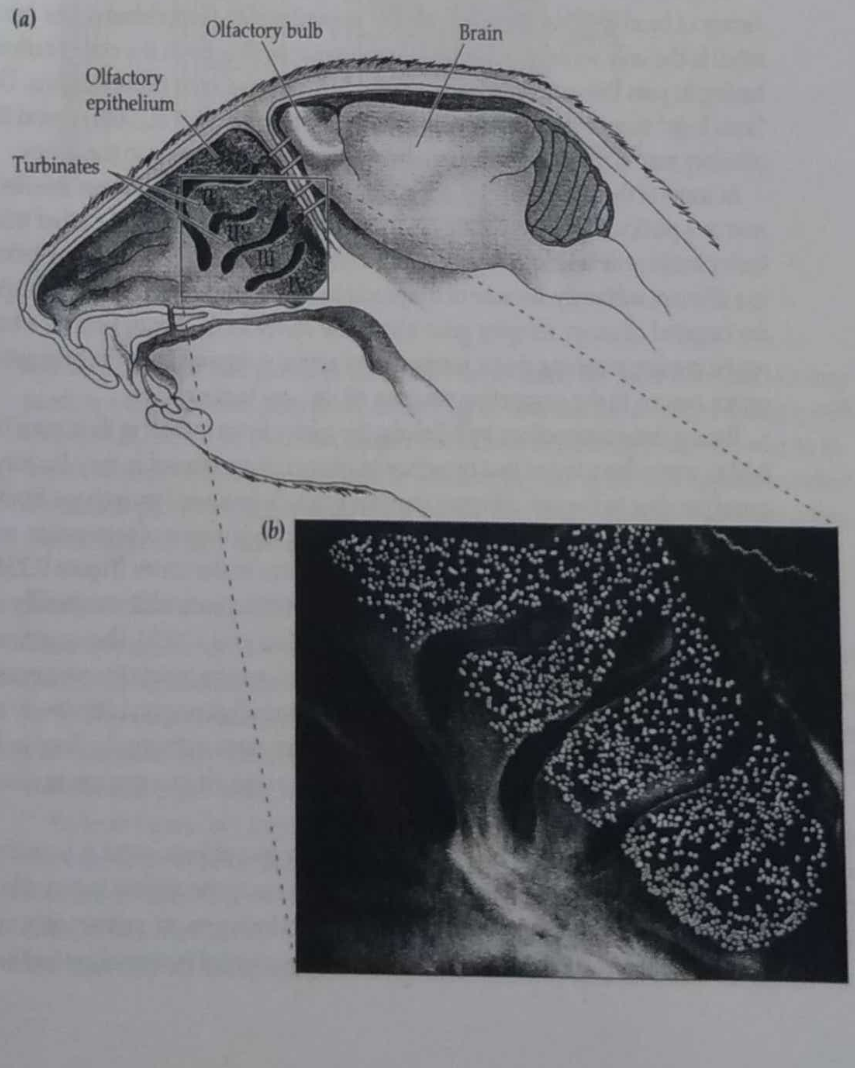
tions of odorants with their receptors trigger the synthesis of second messengers, including cyclic AMP (cAMP) and inositol trisphosphate (IP_3). Cyclic AMP opens a cation channel (Brunet et al., 1996) to elicit the generator current that depolarizes the olfactory receptor cell, and the depolarization in turn leads to action potentials.

This sensory transduction process, portrayed in **Figure 9.21**, is similar to the activation of other sensory systems, such as those for sweet and bitter tastes, and those in the eye (see Chapter 10). A specific G protein, named G_{olf} in recognition of its importance in olfaction, must be used by all the olfactory receptors because mice in which the gene that encodes G_{olf} is knocked out are generally anosmic (Belluscio et al., 1998).

Mice have about 2 million olfactory receptor cells, each of which expresses only one of about 1000 different receptor proteins. These receptor proteins can be divided into four different subfamilies of about 250 proteins each (Mori et al., 1999). Within each subfamily, members have a very similar structure and presumably recognize similar odorants. Each subfamily of receptors is synthesized in a separate band of the epithelium (**Figure 9.22**) (Vassar et al., 1993).

Now that it has been fully mapped, we know that the human genome also contains about 1000 apparent olfactory receptor genes, spread across almost all of the chromosomes, but only about 350 of these appear to be fully functional (Crasto et al., 2001; Glusman et al., 2001). The rest have apparently accumulated mutations and become nonfunctional during the course of evolution, implying that whatever they detected ceased to be important to our ancestors' survival and reproduction.

Since humans can discriminate about 5000 odors, each of the 350 functional odorant receptors must interact with a number of different odorants. Although some odorants may be "recognized" by a single kind of receptor molecule, most odorants probably are recognized by the combination of a few different kinds of receptor molecules.



9.22 Different Kinds of Olfactory Receptor Molecules on the Olfactory Epithelium (a) In this diagram showing the anatomy of the rat olfactory organ, the Roman numerals designate different turbinates. (*b*) The different colors in this photograph of rat olfactory epithelium show receptor locations for four receptor subfamilies (and also correspond to those on the olfactory bulb, which illustrate the probable topographic innervation of that structure). The different receptor types have distinct but overlapping spatial distributions. (After Vassar et al., 1993; *b* courtesy of Robert Vassar.)

In other words, most odorants activate a characteristic array of receptor cells (Duchamp-Viret et al., 1999), and pattern coding identifies odorants.

Olfactory axons connect with the olfactory bulb, which sends its output to several brain regions

The numerous axons of the olfactory nerve terminate in a complex structure at the anterior end of the brain called the **olfactory bulb** (see Figures 9.20 and 9.22). The olfactory bulb is organized into many roughly spherically shaped neural circuits called **glomeruli** (singular *glomerulus*; from the Latin *glomus*, "ball"), within which the axon terminals of olfactory neurons synapse on the dendrites of the specialized **mitral cells** of the olfactory bulb (see Figure 9.20). The intrinsic circuitry within and between these glomeruli contributes to an elaborate system for modulating, tuning, and sharpening olfactory bulb activity (Aungst et al., 2003).

Mice have about 1800 glomeruli. Each one receives inputs exclusively from olfactory neurons that are expressing the same type of olfactory receptor, and the glomeruli are organized in functional zones according to the four receptor protein subfamilies described in the previous section (Mori et al., 1999). So there appears to be a topographic distribution of smells in the bulb, and within each functional zone, neighboring glomeruli tend to receive inputs from receptors that are closely related.

Perhaps surprisingly, olfactory receptors are found in the axon terminals of olfactory neurons, as well as in their dendrites (Barnea et al., 2004). Experiments with knockout mice (see Box 7.3) suggest that olfactory receptor proteins help guide the innervating axons to their corresponding glomeruli. Disruptions of the receptor protein prevent newly generated olfactory receptor axons from reaching their normal targets (F. Wang et al., 1998). The olfactory bulb, in relation to the rest of the brain, is much smaller in humans than in animals such as rats that depend extensively on olfaction (compare Figures 9.20 and 9.22).

Outputs from the olfactory bulb, which are the axons of the mitral cells, extend to a variety of brain regions. These include the prepyriform and entorhinal cortex (note that smell is the only sensory modality that can synapse directly in the cortex rather than having to pass through the thalamus), the amygdala, and the hypothalamus. Using a "knock-in" mouse model, Linda Buck and coworkers (Zou et al., 2001) found that an olfactory map is maintained throughout the olfactory projections to the cortex.

In some of these mice, the gene for a substance called *barley lectin* was inserted right next to a particular gene encoding one type of olfactory receptor. In the other mice, the barley lectin gene was knocked in beside a different olfactory receptor gene belonging to a different subfamily. Because of the proximity of the genes, any neuron that expressed the targeted olfactory receptor gene also made barley lectin. Barley lectin is a transsynaptic marker, meaning that it is transferred across synapses, from the originating receptor neuron to the connecting neurons, all the way to the cortex.

Tracing these connections by following the barley lectin marker in their mice (**Figure 9.23*a***), researchers found that two discrete glomeruli are labeled in the olfactory bulb, corresponding to the two different receptor types. Subsequent projections from these glomeruli to olfactory cortical sites maintained their high degree of segregation and terminated in stereotyped, partially overlapping patterns in the cortex (**Figure 9.23*b***). The olfactory projections form highly complex maps in the cortex, with structurally related substances represented in neighboring regions (Zou et al., 2005). These cortical odor maps are very similar between individual mice and may be innate to some extent. Interestingly, the olfactory cortex also contains neurons that respond selectively to *mixtures* of receptor-specific odorants, but not to the odorants individually (Zou and Buck, 2006). This may explain why blends of substances, as in perfume, can create unique olfactory experiences.

Functional-MRI studies suggest that the human prepyriform cortex is activated during sniffing, whether or not an odor is present, because the airflow induced by sniffing provides somatosensory stimulation. When an odor is present, primary olfactory cortex (prepyriform cortex) and secondary olfactory cortex (orbitofrontal cortex) are both

olfactory bulb An anterior projection of the brain that terminates in the upper nasal passages and, through small openings in the skull, provides receptors for smell.

glomerulus A complex arbor of dendrites from a group of olfactory cells.

mitral cell A type of cell in the olfactory bulb that conducts smell information from the glomeruli to the rest of the brain.

In other words, most odorants activate a characteristic array of receptor cells (Duchamp-Viret et al., 1999), and pattern coding identifies odorants.

Olfactory axons connect with the olfactory bulb, which sends its output to several brain regions

The numerous axons of the olfactory nerve terminate in a complex structure at the anterior end of the brain called the **olfactory bulb** (see Figures 9.20 and 9.22). The olfactory bulb is organized into many roughly spherically shaped neural circuits called **glomeruli** (singular *glomerulus*; from the Latin *glomus*, "ball"), within which the axon terminals of olfactory neurons synapse on the dendrites of the specialized **mitral cells** of the olfactory bulb (see Figure 9.20). The intrinsic circuitry within and between these glomeruli contributes to an elaborate system for modulating, tuning, and sharpening olfactory bulb activity (Aungst et al., 2003).

Mice have about 1800 glomeruli. Each one receives inputs exclusively from olfactory neurons that are expressing the same type of olfactory receptor, and the glomeruli are organized in functional zones according to the four receptor protein subfamilies described in the previous section (Mori et al., 1999). So there appears to be a topographic distribution of smells in the bulb, and within each functional zone, neighboring glomeruli tend to receive inputs from receptors that are closely related.

Perhaps surprisingly, olfactory receptors are found in the axon terminals of olfactory neurons, as well as in their dendrites (Barnea et al., 2004). Experiments with knockout mice (see Box 7.3) suggest that olfactory receptor proteins help guide the innervating axons to their corresponding glomeruli. Disruptions of the receptor protein prevent newly generated olfactory receptor axons from reaching their normal targets (F. Wang et al., 1998). The olfactory bulb, in relation to the rest of the brain, is much smaller in humans than in animals such as rats that depend extensively on olfaction (compare Figures 9.20 and 9.22).

Outputs from the olfactory bulb, which are the axons of the mitral cells, extend to a variety of brain regions. These include the prepyriform and entorhinal cortex (note that smell is the only sensory modality that can synapse directly in the cortex rather than having to pass through the thalamus), the amygdala, and the hypothalamus. Using a "knock-in" mouse model, Linda Buck and coworkers (Zou et al., 2001) found that an olfactory map is maintained throughout the olfactory projections to the cortex.

In some of these mice, the gene for a substance called *barley lectin* was inserted right next to a particular gene encoding one type of olfactory receptor. In the other mice, the barley lectin gene was knocked in beside a different olfactory receptor gene belonging to a different subfamily. Because of the proximity of the genes, any neuron that expressed the targeted olfactory receptor gene also made barley lectin. Barley lectin is a transsynaptic marker, meaning that it is transferred across synapses, from the originating receptor neuron to the connecting neurons, all the way to the cortex.

Tracing these connections by following the barley lectin marker in their mice (**Figure 9.23*a***), researchers found that two discrete glomeruli are labeled in the olfactory bulb, corresponding to the two different receptor types. Subsequent projections from these glomeruli to olfactory cortical sites maintained their high degree of segregation and terminated in stereotyped, partially overlapping patterns in the cortex (**Figure 9.23*b***). The olfactory projections form highly complex maps in the cortex, with structurally related substances represented in neighboring regions (Zou et al., 2005). These cortical odor maps are very similar between individual mice and may be innate to some extent. Interestingly, the olfactory cortex also contains neurons that respond selectively to *mixtures* of receptor-specific odorants, but not to the odorants individually (Zou and Buck, 2006). This may explain why blends of substances, as in perfume, can create unique olfactory experiences.

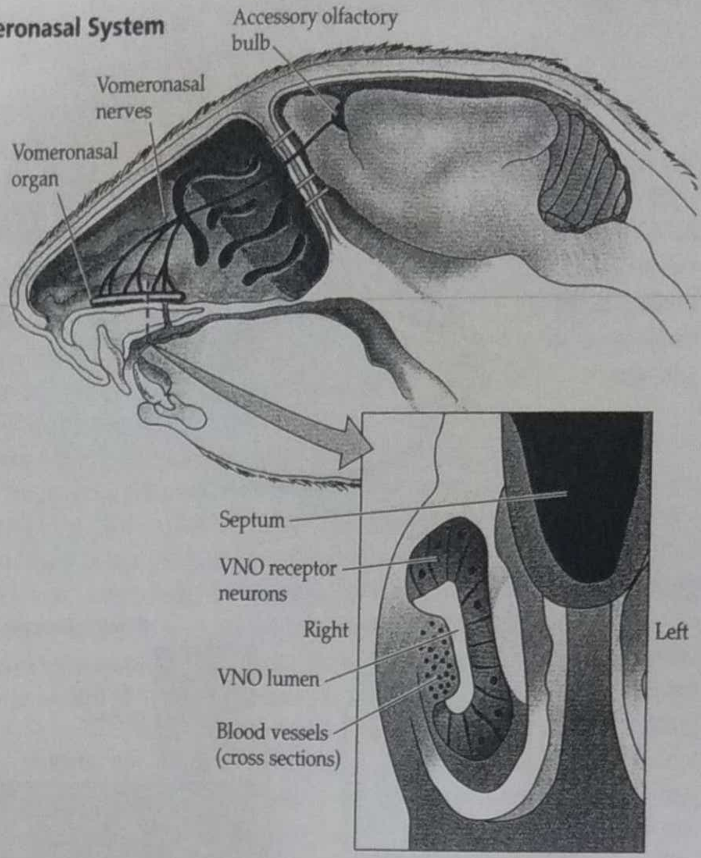
Functional-MRI studies suggest that the human prepyriform cortex is activated during sniffing, whether or not an odor is present, because the airflow induced by sniffing provides somatosensory stimulation. When an odor is present, primary olfactory cortex (prepyriform cortex) and secondary olfactory cortex (orbitofrontal cortex) are both

olfactory bulb An anterior projection of the brain that terminates in the upper nasal passages and, through small openings in the skull, provides receptors for smell.

glomerulus A complex arbor of dendrites from a group of olfactory cells.

mitral cell A type of cell in the olfactory bulb that conducts smell information from the glomeruli to the rest of the brain.

9.24 The Vomeronasal System



tribution of certain V2Rs differs between male and female rats, in keeping with the critical role of pheromones in organizing rodent reproductive behavior (Herrada and Dulac, 1997). V2Rs are also sensitive to certain major histocompatibility complex (MHC) molecules (Loconto et al., 2003); detection of MHCs is thought to be one of the main ways in which animals can assess their degree of relatedness to other animals, which has implications for mating strategies (see Chapter 6). A VNO-specific ion channel called *TRP2* (*transient receptor potential 2*)—a member of the TRP family of sensory receptors that we mentioned earlier—is also essential for VNO function (Stowers et al., 2002).

VNO receptors are remarkably sensitive, detecting extremely low concentrations of pheromone molecules (Leinders-Zufall et al., 2000). The receptors send their information to the accessory olfactory bulb (adjacent to the main olfactory bulb), which projects to the medial amygdala, which in turn projects to the hypothalamus. Relying in part on MHCs, hamsters (Mateo and Johnston, 2000) and mice (Isles et al., 2001) can distinguish relatives from nonrelatives just by smell, even if they were raised by foster parents. Presumably they compare whether other animals smell like themselves, perhaps to avoid mating with kin.

The VNO is usually said to be absent or vestigial in fishes, birds, and higher primates. (M. Halpern, 1987). In humans, molecular and anatomical evidence for a functional VNO is scanty at best. Although humans have a structure that resembles a VNO, analysis of the genome indicates that almost all of the human variants of the genes that encode the V1R and V2R vomeronasal receptors are nonfunctional, as is the gene that encodes the TRP2 ion channel.

Despite our apparent lack of a functional VNO, some behavioral evidence indicates that humans are sensitive to certain pheromones. For example, exposure to extracts of sweat, when applied to the upper lip of women, produce systematic changes in the menstrual cycles of the recipients that reflect the menstrual phase of the sweat *donors* (K. Stern and McClintock, 1998). Other studies have suggested that humans are sensitive to MHCs and may alter their social behavior and attraction to potential mates on this basis.

The recent discovery of a new class of olfactory receptors within the main olfactory epithelium (Liberles and Buck, 2006) may finally resolve the question of human pheromone sensitivity. Called **TAARs** (for **trace amine-associated receptors**), these receptors are expressed in specific olfactory neurons within the main olfactory epithelium, just like the regular olfactory receptors, but they respond to probable pheromones instead of odorants. In mice, five of the nine TAARs that have been identified respond to volatile substances found in mouse urine; one of these is specifically activated by urine from adult males, but not urine from females or juvenile males. Other studies have shown that the secretion of gonadotropins (crucial for sexual behavior) is regulated primarily by projections from the main olfactory epithelium, not the vomeronasal organ (Yoon et al., 2005). This observation provides additional evidence that the main olfactory epithelium also detects pheromones to organize behavior. It seems likely that similar mechanisms will be identified in the human olfactory system.

trace amine-associated receptors (TAARs) A family of probable pheromone receptors found in the main olfactory epithelium.

Summary

Hearing

1. The external ear captures, focuses, and filters sound. The sound arriving at the tympanic membrane (eardrum) is focused by the ossicles of the middle ear onto the oval window to stimulate the fluid-filled inner ear (cochlea).
2. Sound arriving at the oval window causes traveling waves to sweep along the basilar membrane of the inner ear. For high-frequency sounds, the largest displacement of the basilar membrane is at the base of the cochlea, near the oval window; for low-frequency sounds, the largest amplitude is near the apex of the cochlea.
3. The organ of Corti has both inner hair cells (about 3500 in humans) and outer hair cells (about 12,000 in humans). The inner hair cells convey most of the information about sounds. The outer hair cells change their length under the control of the brain, amplifying the movements of the basilar membrane in response to sound and sharpening the frequency tuning of the cochlea.
4. Movement of the stereocilia of the hair cells causes the opening and closing of ion channels, thereby transducing mechanical movement into changes in electrical potential. These changes in potential stimulate the nerve cell endings that contact the hair cells.
5. At each level of the auditory system, sound frequencies are mapped in an orderly succession; this is called tonotopic mapping.
6. Two theories explain the discrimination of auditory frequency. According to place theory, our perception of pitch depends on where the sound causes maximal displacement of the basilar membrane. Volley theory argues that the relations between the frequencies of auditory stimuli and the pattern or timing of neural discharges are the important criteria for pitch discrimination. In practice, we appear to use both of these encoding systems to determine pitch.
7. Auditory localization depends on differences in the sounds arriving at the two ears. For low-frequency sounds, differences in time of arrival at the two ears are especially important. For high-frequency sounds, differences in intensity are especially important. Birds and mammals evolved different neural mechanisms for localizing sounds; in mammals the lateral superior olivary nucleus of the brainstem processes differences in intensity, and the medial superior olivary nucleus processes differences in time of arrival. Spectral filtering performed by the external ear provides elevation cues.
8. Primary auditory cortex is specialized for processing complex, biologically important sounds, rather than pure tones.
9. Experiences with sound early in life can influence later auditory localization and the responses of neurons in auditory pathways. Experiences later in life can also lead to changes in responses of auditory neurons. Some cortical areas are polymodal and help calibrate the auditory system through the use of other senses.
10. Deafness can be caused by changes at any level of the auditory system. Conduction deafness consists of impairments in the transmission of sound through the external or middle ear to the cochlea. Sensorineural deafness arises in the cochlea, often because of the destruction of hair cells, or in the auditory nerve. Central deafness stems from brain damage.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

CHAPTER 10

CONTENTS

Vision Provides Information about the Form, Color, Location, Movement, and Identity of Objects 285

The Visual System Extends from the Eye to the Brain 289

The Eye Is Both an Optical Device and a Neural Organ 289

Neural Signals Travel from the Retina to Several Brain Regions 299

Neurons at Different Levels of the Visual System Have Very Different Receptive Fields 300

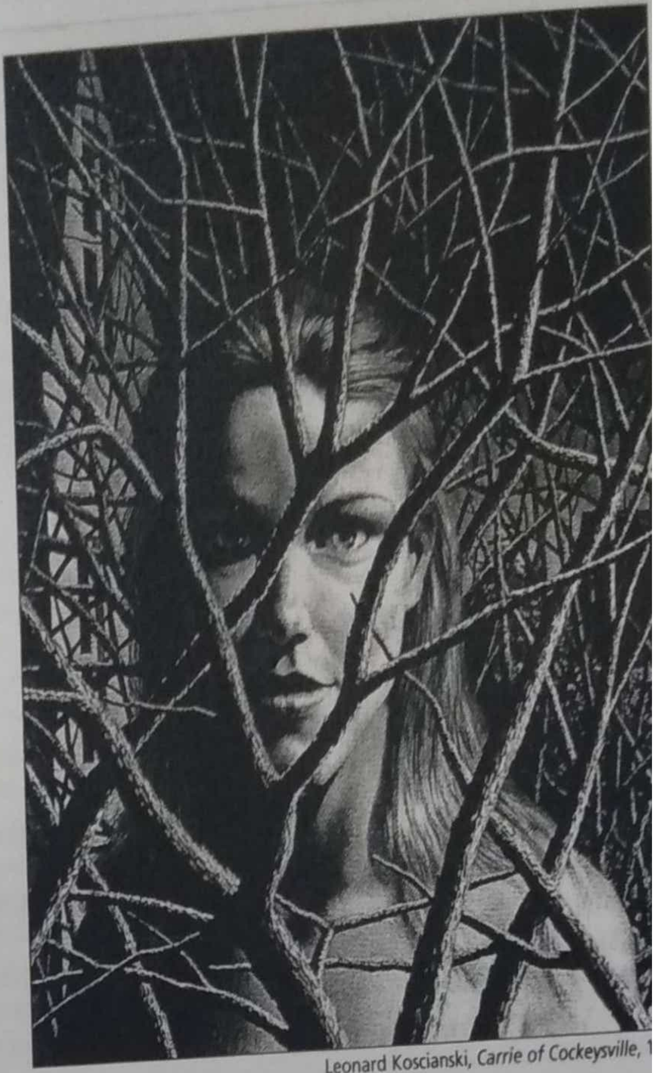
Area V1 Is Organized in Columns and Slabs 308

Color Vision Depends on Special Channels from the Retinal Cones through Cortical Area V4 310

Perception of Visual Motion Is Analyzed by a Special System That Includes Cortical Area V5 314

The Many Cortical Visual Areas Are Organized into Two Major Systems 314

Visual Neuroscience Can Be Applied to Alleviate Some Visual Deficiencies 316



Leonard Koscianski, *Carrie of Cockeysville*,

Vision: From Eye to Brain

When Seeing Isn't Seeing

It was cold in the bathroom, so the young woman turned on a small heater before she got in the shower. She didn't know that the heater was malfunctioning, filling the room with deadly, odorless carbon monoxide gas. Her husband found her unconscious on the floor and called for an ambulance to rush her to the emergency room. When she regained consciousness, "D.F." seemed to have gotten off lightly, avoiding what could have been a fatal accident. She could understand the doctors' questions and reply sensibly, move all her limbs, and perceive touch on her skin, but something was wrong with her sight.

D.F. couldn't recognize faces, even her husband's, nor could she name any objects presented to her view. D.F. still cannot recognize objects today, more than 15 years after her accident. Yet she is not entirely blind. Show her a flashlight and she can tell you that it's made of shiny aluminum with some red plastic, but she doesn't recognize it ("Is it a kitchen utensil?"). Without telling her what it is, if you ask her to pick it up, D.F.'s hand goes directly to the flashlight and holds it exactly as one normally holds a flashlight. Show D.F. a slot in a piece of plastic and she cannot tell you whether the slot is oriented vertically, horizontally, or diagonally; but if you hand her a disk and ask her to put it through the hole, D.F. invariably turns the disk so that it goes smoothly through the slot (Goodale et al., 1991).

Can D.F. see or not?

Vision offers tremendous benefits for vital behaviors such as finding food, avoiding predators, finding a mate, and locating shelter, so a variety of visual systems—different in some respects but similar in others—have evolved. Beyond serving basic needs, vision affords most of us the pleasures of nature and art, reading and writing, and watching films and TV. Because vision is so important, much effort is expended to improve it, to prevent its deterioration, and even to restore vision to the blind.

However, the sheer volume of visual information poses a serious problem. Seeing the surrounding world has been compared to drinking from a waterfall. How does the visual system avoid being overwhelmed by the flood of information that enters the eyes? The answer seems to be that the visual perceptions of each species depend on how their eyes and brains evolved to process information about light and attend to the aspects likely to be important for their survival.

Different kinds of processing allow us to see the form, color, position, and distance of objects in the visual field and to recognize objects. Research on vision is one of the most active fields of biological psychology and neuroscience, as it should be, since about one-third of the human cerebral cortex is devoted to visual analysis and perception.

Vision Provides Information about the Form, Color, Location, Movement, and Identity of Objects

Although we're familiar with vision because we use it every day, some features of visual perception are not immediately apparent. Highlighting some of our visual abilities will help us understand the accomplishments of the visual system.

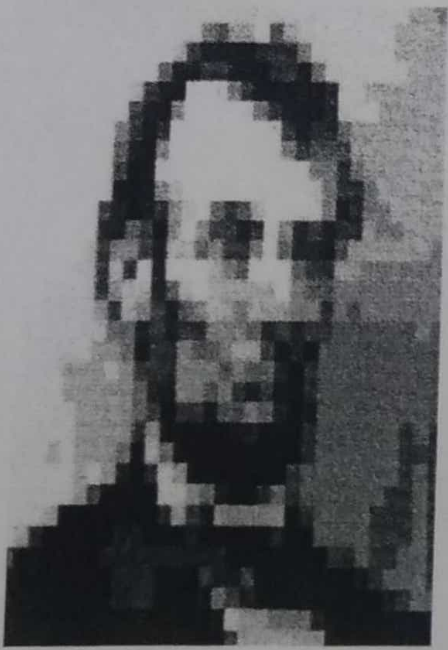
```
9 9 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 7 7 6
9 9 8 8 9 8 9 8 8 8 8 8 8 8 6 5 7 7 9 5 7 8 8 8 8 8 8 8 7 7 7 7
9 9 8 9 9 9 9 9 9 9 9 9 7 4 3 3 3 3 4 4 4 6 8 8 8 8 8 8 7 7 7 7
9 9 8 8 9 9 9 9 9 9 8 5 3 3 4 4 3 3 3 4 4 3 6 8 8 8 8 8 8 7 7 7
9 9 9 8 8 8 8 8 8 7 4 3 3 8 9 9 6 4 3 3 3 3 3 4 8 8 7 7 7 7 7 7
9 9 9 8 8 8 8 8 8 4 3 3 6 9 9 9 9 8 6 4 3 3 3 4 8 8 8 7 7 7 7 7
9 9 9 9 8 8 8 8 6 4 3 4 9 9 9 9 9 9 9 8 4 3 4 4 6 7 7 7 7 7 7 7
9 9 8 8 8 8 8 8 5 3 3 6 9 9 9 9 9 9 9 9 6 4 5 5 5 7 7 7 7 7 7 7
9 9 8 8 8 8 8 8 4 2 3 8 8 9 9 9 9 9 9 9 9 8 6 6 4 6 7 7 7 7 7 7
9 9 8 8 8 8 8 8 2 2 3 6 7 9 9 9 9 9 9 8 8 9 8 6 4 4 6 7 7 7 7 7
9 9 8 8 8 8 8 4 3 2 3 4 6 7 8 5 4 5 7 8 8 8 8 6 3 4 6 6 7 7 7 7
9 9 8 8 8 8 8 3 3 5 4 2 6 8 6 4 4 3 4 8 6 3 4 3 4 4 7 6 6 7 7 7
9 9 8 8 8 8 7 4 6 6 4 3 7 7 5 6 4 4 6 8 5 3 3 3 5 7 7 7 7 7 7 6
9 9 8 8 8 7 7 4 7 4 8 3 8 8 8 7 6 5 8 8 8 5 4 4 7 7 6 6 6 6 6 6
9 8 8 7 7 7 7 4 6 7 7 3 5 7 8 7 7 7 7 7 8 6 5 5 6 6 6 6 6 6 6 6
9 8 7 7 7 7 7 6 4 7 6 4 3 5 6 7 7 6 7 7 7 6 6 4 6 5 6 6 6 6 6 6
9 8 7 7 7 7 7 7 5 5 3 4 3 4 4 6 6 6 5 3 4 3 4 4 5 5 5 5 5 5 6 5
9 8 7 7 7 7 7 6 6 5 2 4 4 6 5 5 6 7 7 4 2 3 2 5 5 5 5 5 5 5 5 5
9 8 7 7 7 6 6 6 7 6 4 4 4 6 6 6 5 6 5 5 3 2 4 5 5 5 5 5 5 5 5 5
9 7 7 7 7 6 6 6 6 6 5 3 3 6 6 5 6 4 3 4 2 2 4 5 5 5 5 5 5 5 5 5
9 7 7 7 7 7 6 6 6 6 5 4 2 4 4 3 5 5 6 5 3 2 3 5 5 5 5 5 5 5 5 5
9 7 7 7 7 7 6 6 6 6 4 6 2 2 2 2 3 3 2 2 2 4 5 5 5 5 5 5 5 4 5 4
9 7 7 7 6 7 6 6 6 5 2 7 5 2 2 2 2 2 2 2 2 2 4 5 5 5 5 5 5 4 4 4
9 7 7 7 7 7 6 7 6 3 2 4 7 6 2 2 2 2 2 2 2 2 4 5 5 5 5 5 5 4 5 4
9 7 7 7 7 7 6 4 2 2 2 2 7 7 6 5 3 2 2 4 5 4 5 5 5 5 5 5 4 4 5 4
9 7 7 7 6 2 2 2 2 2 2 2 4 6 4 3 6 6 6 6 6 2 4 5 5 5 5 4 4 4 5 4
9 7 6 3 2 2 2 2 2 3 3 2 2 2 3 2 2 2 2 2 3 2 2 5 5 5 5 4 4 4 5 4
8 4 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 2 2 2 2 2 2 2 4 4 5 4 4 5 5 4
8 2 2 2 2 2 2 2 2 3 3 3 2 2 2 4 3 3 4 2 2 2 2 2 2 2 3 4 5 5 5 4
8 2 2 2 2 2 2 2 2 3 3 3 2 2 2 3 5 4 3 2 2 2 2 2 2 2 2 2 3 4 5 5
6 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 7 6 6 5 5 5 3 2 2 2 2 2 2 2 3
6 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 4 6 6 6 6 6 6 2 2 2 2 2 2 2 2
```

10.1 Can You Identify the Subject? This array of numbers represents the point-to-point illumination of a picture, with each number representing a particular shade of gray from darkest (2) to lightest (9).

visual field The whole area that you can see without moving your head or eyes.

visual acuity Sharpness of vision.

photoreceptors Neural cells in the retina that respond to light.



10.2 The Subject of Figure 10.1

Perception of form and identification of objects are complex accomplishments

The whole area that you can see without moving your head or eyes is called your **visual field**. In a single glance, you perceive the details of objects accurately only in the center of your visual field. We are usually not aware of this phenomenon because we move our gaze rapidly as we scan a scene or read text. Thus we build up a sort of collage of detailed views. But try keeping your eyes fixed on a letter in the center of a line and then attempt to read a word on the opposite page. You'll find it difficult because **visual acuity** (the sharpness of vision) falls off rapidly from the center of the visual field toward the periphery. This difference in acuity across the visual field is the reason your gaze has to jump from place to place in a line as you read.

If a stimulus suddenly appears away from the center of the visual field, we shift our view, placing the new stimulus in the center of the visual field, where we can see it clearly. When we examine the circuitry of the retina and of higher stations of the visual system a little later, we will learn why vision is so much more acute in the center of the visual field.

We perceive a simple form like a triangle or recognize the face of a friend so rapidly and easily that we do not appreciate that these are exceedingly complex events that require processing in several parts of the brain. Most of the forms we see are embedded in complicated fields of objects; extracting a particular form for attention and identification requires practice and skill. It has been very difficult for artificial systems to achieve even primitive recognition of objects. Furthermore, recognition requires more than the accurate perception of objects. For example, some people with brain damage, like D.F., lose their ability to recognize familiar faces or objects, even though they can still describe them accurately.

Consider the complexity of visual perception at the level of the nervous system. The retina, a sheet of tissue covering the inside of the eye, contains about 100 million light-sensitive receptor cells (called **photoreceptors**). At any given moment, each retinal receptor is in a particular state of excitation that can be represented numerically. About three times per second, the nervous system surveys the values of all the millions of photoreceptors. It then faces the stupendous task of trying to figure out what in the outside world could have produced that particular array of values.

Figure 10.1 illustrates a simple example of such a task. The numbers in this array represent shades of gray from darkest (2) to lightest (9). As you inspect this grid, you may notice that the numbers representing lighter shades appear mainly in the upper half of the array, but you don't perceive a familiar form.

Now look at **Figure 10.2**, which shows the shades of gray that correspond to the numbers in the array in Figure 10.1; the form and identity leap out. Your nervous system processes data such as those in Figure 10.1 to achieve the perception of the form in Figure 10.2 in an instant. How the nervous system processes so much data so quickly is the staggering problem that confronts anyone who tries to understand vision.

It appears that we have to learn how to recognize faces and objects. Furthermore, this ability can be lost after years without sight, as shown by the case of Michael May described in Chapter 7 (Fine et al., 2003). In fact, as we'll see, not only object recognition but also color, brightness, motion, and other aspects of visual perception do not come directly from the retinal image. Rather, the retinal stimuli trigger responses determined by the consequences of the individual's prior interactions with the environment. That is, "the observer sees the probability distribution of the possible sources of the visual stimulus" (Purves and Lotto, 2003, p. 227).

Color is created by the visual system

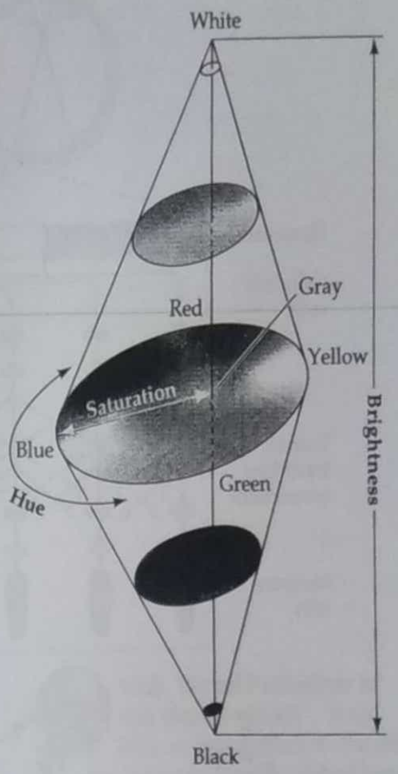
For most of us, the visible world has several distinguishable hues: blue, green, yellow, red, and their intermediates. These hues appear different because the reflected light that reaches our eyes can vary in wavelength (**Box 10.1**), and we can detect some of these differences. For about 8% of human males and about 0.5% of females, however, some of these color distinctions are either absent or at least less striking.

Although the term *color blindness* is commonly used, most people with impaired color vision are able to distinguish some hues. Complete color blindness in humans is extremely rare, although it can be caused by brain lesions or by the congenital absence of specialized receptors. Animals exhibit different degrees of color vision. Many species of birds, fishes, and insects have excellent color vision. Humans and Old World monkeys also have an excellent ability to discriminate wavelengths, but many other mammals (e.g., cats) cannot discriminate wavelengths very well. We'll see more about the distribution of color vision among mammals later in this chapter.

A patch of light has other qualities besides hue. The color solid shown in **Figure 10.3** illustrates the basic dimensions of our perception of light; the figure is deliberately asymmetrical, for reasons we will explain. The three dimensions of color are

1. **Brightness**, which varies from dark to light; it is represented by the vertical dimension in Figure 10.3. Planes are shown intersecting the figure at different levels of brightness. The planes are tipped up for yellow and down for blue because yellow is perceived as lighter and blue as darker than the other hues.
2. **Hue**, which varies continuously around the color circle through blue, green, yellow, orange, and red. (Hue is what most people mean when they use the term *color*.)
3. **Saturation**, which varies from rich, full colors at the periphery of the color solid to gray at the center. For example, starting with red at the periphery, the colors become paler toward the center, going through pink to gray. Yellow is shown closer to the central axis than the other saturated hues because yellow is perceived as less saturated than the other hues.

It is important not to equate perception of a particular hue with a particular stimulus (a wavelength of light), because a patch illuminated by a particular wavelength is seen as various different hues, depending on factors such as the intensity of illumination, the surrounding field, and prior exposure to a different stimulus. As illumination fades, the blues in a painting or a rug appear more prominent and the reds appear duller, even though the wavelength distribution in the light has not changed. In addition, the hue perceived at a particular point is strongly affected by the pattern of wavelengths and intensities in other parts of the visual field.



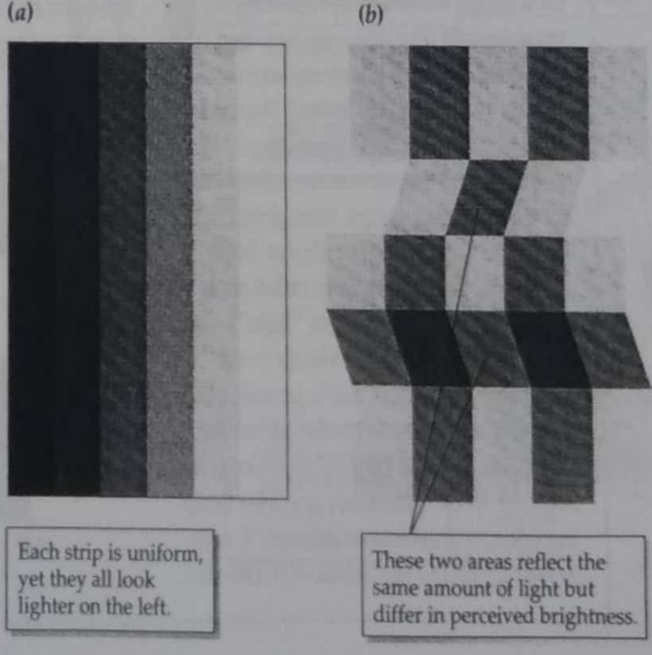
10.3 The Color Solid The three basic dimensions of the perception of light are brightness, hue, and saturation.

Brightness is created by the visual system

The brightness dimension of visual perception is created in part by the visual system, not simply by the amount of light reflected. Figure 10.4 presents two examples. The enhancement of the boundaries of the bars in **Figure 10.4a**, each of which is uniformly gray but looks as though it varies in brightness, is based on a neural process called **lateral inhibition**.

Lateral inhibition occurs where the neurons in a region—in this case, retinal cells—are interconnected, either through their own axons or by means of intermediary neurons (interneurons), and each neuron tends to inhibit its neighbors (**Figure 10.5**). Lateral inhibition occurs in the skin senses too; if you

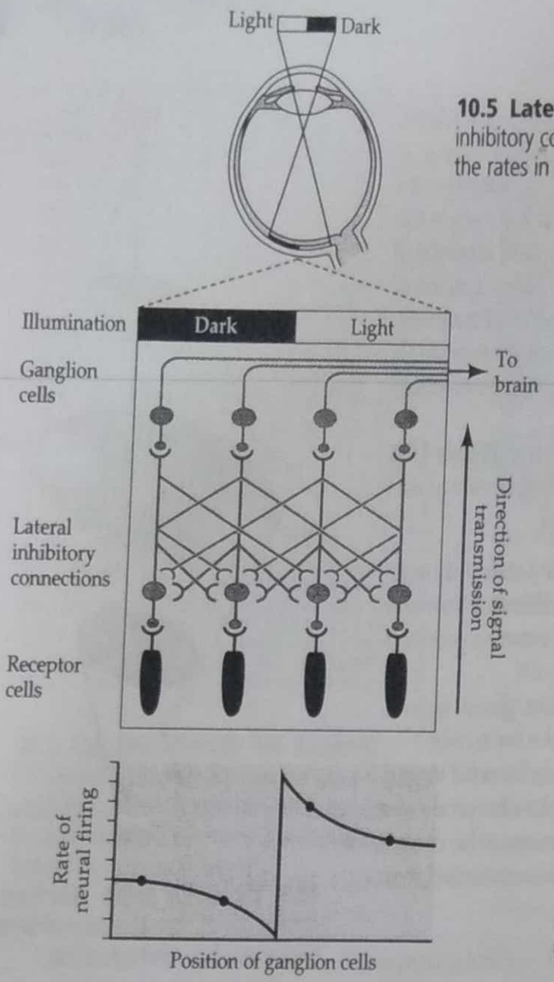
lateral inhibition The phenomenon by which interconnected neurons inhibit their neighbors, producing contrast at the edges of regions.



Each strip is uniform, yet they all look lighter on the left.

These two areas reflect the same amount of light but differ in perceived brightness.

10.4 The Effect of Context on the Perception of Brightness (*a*) Although each of the four central bars shown here is uniform in color, each appears lighter on the left and darker on the right. (*b*) Shading around a patch of light affects the perception of brightness. For example, even though the two indicated patches are the same shade of gray, one appears darker than the other. If you don't believe this, punch two holes 15 mm apart on a piece of white paper, put the holes over the two areas, and compare them again. (Part *b* from Adelson, 1993.)


Light
Dark
Illumination
Dark
Light
Ganglion cells
To brain
Lateral inhibitory connections
Receptor cells
Direction of signal transmission
Rate of neural firing
Position of ganglion cells

10.5 Lateral Inhibition in the Retina As the graph shows, because of the lateral inhibitory connections the rates of firing in the two central receptor cells are more different than the rates in the two receptor cells on either side.

press the end of a ruler against the skin of your forearm, for example, you will probably feel the pressure at the corners of the ruler more strongly than you feel the pressure along the line of contact.

In **Figure 10.4*b***, two patches that clearly differ in brightness *reflect the same amount of light.* If you use your hands to cover the surrounding pattern to the left and right of the two patches, they appear the same. How are such puzzling effects produced? Although the contrast effect in Figure 10.4*a* is determined, at least in part, by interactions among adjacent retinal cells, the two areas indicated in Figure 10.4*b* are not adjacent, so the effect must be produced higher in the visual system (Adelson, 1993).

Motion can enhance the perception of objects

Movement enhances the visibility of objects, which is an important adaptation in the visual system because predators and prey alike must be sensitive to moving objects in order to survive. In the periphery of our visual field, we may not be able to see stationary objects, but we can detect motion. We detect motion only within a range of speed that is appropriate to the locomotion of animals.

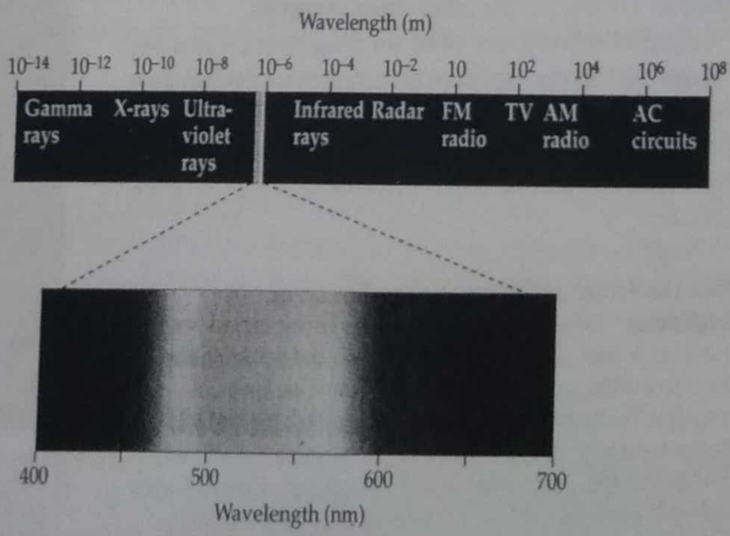
Anything that moves faster is a blur or may be invisible, as is a bullet speeding by. Anything that moves too slowly—such as the hour hand of a clock—is not seen as moving, although we can note from time to time that it has changed position. A succession of still pictures, presented at the

BOX 10.1 The Basics of Light

The physical energy to which our visual system responds is a band of electromagnetic radiation. This radiation comes in very small packets of energy called **quanta** (singular *quantum*). Each quantum can be described by a single number, representing its **wavelength** (the distance between two adjacent crests of vibratory activity).

The human visual system responds only to quanta whose wavelengths lie within a very narrow section of the total electromagnetic range, from about 400 to 700 nm, as the figure shows. Such quanta of light energy are called **photons** (from the Greek *phos*, "light"). The band of radiant energy visible to animals may be narrow, but it provides for accurate reflection from the surface of objects in the size range that matters for survival. Radio waves are good for imaging objects of astronomical size; X-rays penetrate below the surfaces of objects.

Each photon is a very small amount of energy; the exact amount depends on the wavelength. A single photon of wavelength 560 nm contains only a tiny amount of energy. A 100-watt (W) light bulb gives off only about 3 W of visible light; the rest is heat. But even the 3 W of light amounts to 8 quintillion (8×10^{18}) photons per second. When quanta within the visible spectrum enter the eye, they can evoke visual sensations. The exact nature of such sensations depends both on the wavelengths of the quanta and on the number of quanta per second.


Wavelength (m)
10^{-14}
10^{-12}
10^{-10}
10^{-8}
10^{-6}
10^{-4}
10^{-2}
10
10^{2}
10^{4}
10^{6}
10^{8}
Gamma rays
X-rays
Ultra-violet rays
Infrared rays
Radar
FM radio
TV
AM radio
AC circuits
400
500
600
700
Wavelength (nm)

proper rate, can cause apparent motion, as in motion pictures. Perception of motion is analyzed by special areas of the brain, as we will see later in this chapter.

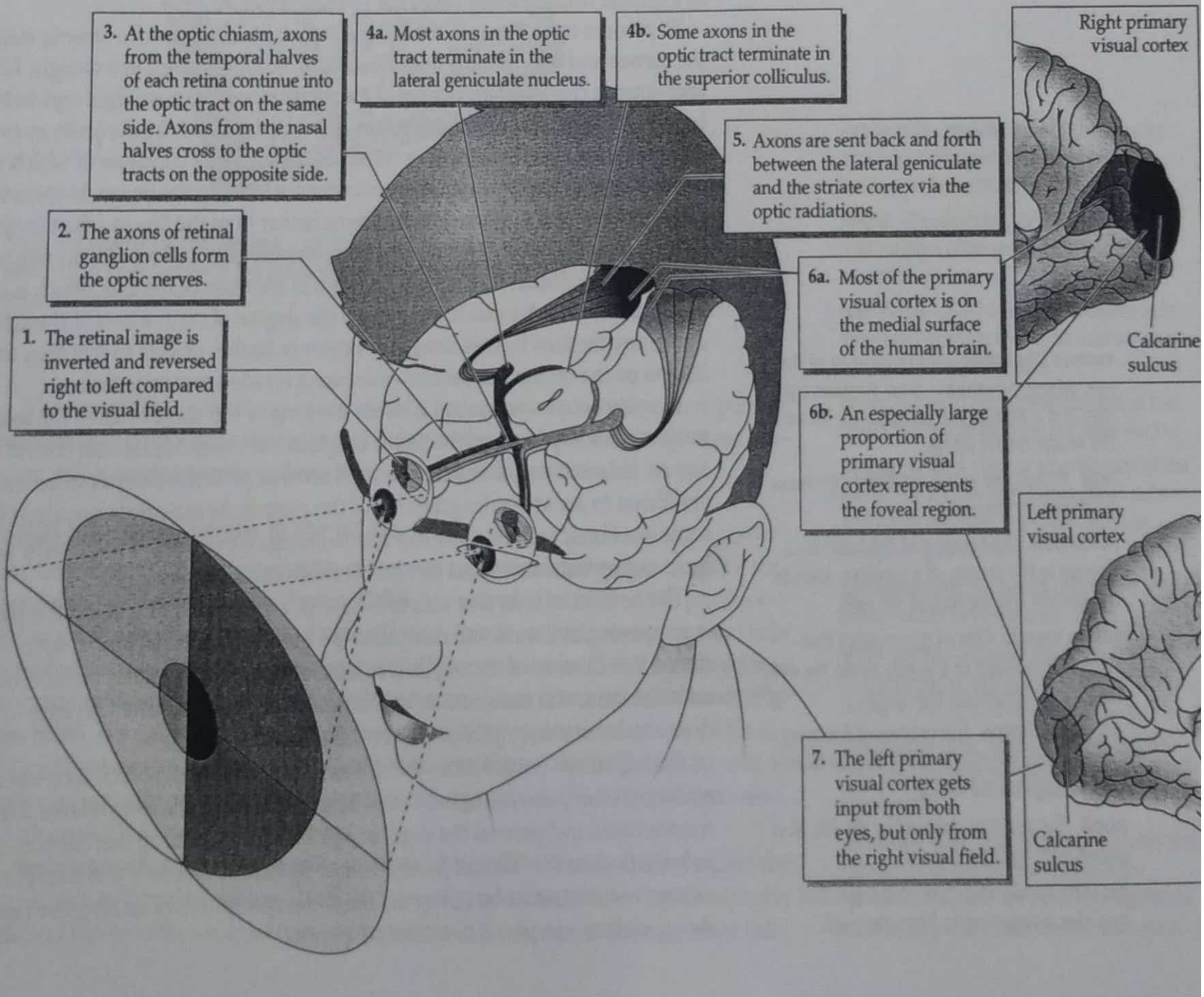
The Visual System Extends from the Eye to the Brain

A large part of the visual system is required to accomplish visual perception. **Figure 10.6** shows the visual pathways, starting at the retina in the eye and leading to the primary visual cortex at the back of the brain. Visual cortical areas beyond the primary visual cortex are also involved in perception. Let's note briefly the successive levels of the visual system, and then we will consider what each level contributes to perception.

The retina is a complex structure with several types of cells in distinct layers, as we will discuss shortly. Receptor cells in the retina transduce visual stimuli into neural signals, and additional retinal cells accomplish initial processing of these signals. The neural signals that result from visual processing in the retina converge on the ganglion cells, whose axons make up the optic nerves (2 in Figure 10.6). Most of these axons terminate in the lateral geniculate nucleus (4a in Figure 10.6), which is part of the thalamus, but some terminate in the superior colliculus (4b) in the midbrain. From the lateral geniculate, fibers of the optic radiations project to the primary visual cortex (6a and 6b).

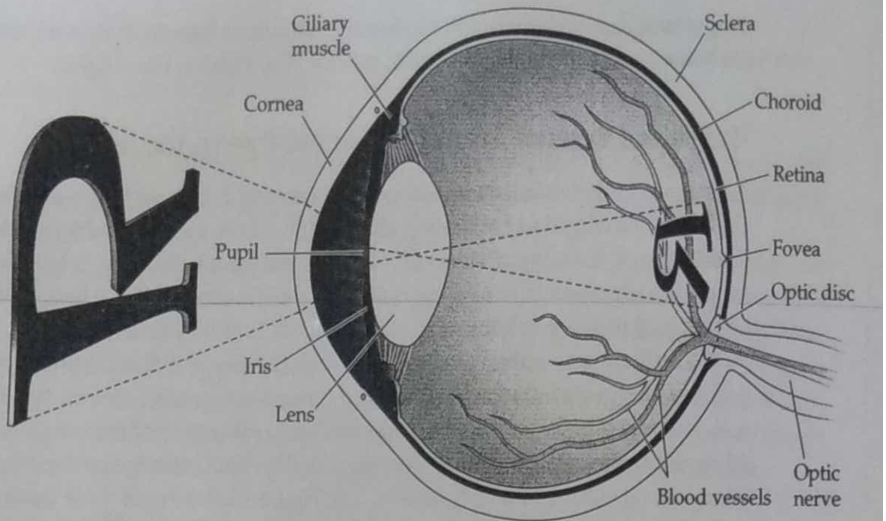
The Eye Is Both an Optical Device and a Neural Organ

The eye is an elaborate structure with optical functions (capturing light and forming detailed spatial images) and neural functions (transducing light into neural signals and processing these signals).



3. At the optic chiasm, axons from the temporal halves of each retina continue into the optic tract on the same side. Axons from the nasal halves cross to the optic tracts on the opposite side.
4a. Most axons in the optic tract terminate in the lateral geniculate nucleus.
4b. Some axons in the optic tract terminate in the superior colliculus.
Right primary visual cortex
5. Axons are sent back and forth between the lateral geniculate and the striate cortex via the optic radiations.
2. The axons of retinal ganglion cells form the optic nerves.
6a. Most of the primary visual cortex is on the medial surface of the human brain.
1. The retinal image is inverted and reversed right to left compared to the visual field.
Calcarine sulcus
6b. An especially large proportion of primary visual cortex represents the foveal region.
Left primary visual cortex
7. The left primary visual cortex gets input from both eyes, but only from the right visual field.
Calcarine sulcus

10.6 Visual Pathways in the Human Brain Visual fields are represented on the retinas and project to the cerebral hemispheres. The right visual field projects to the left cerebral hemisphere; the left visual field, to the right cerebral hemisphere.



10.7 Structures of the Human Eye Here the right eye is viewed in cross section from above. The visual image focused on the retina is inverted top to bottom and reversed right to left. The gap in the retina where the optic nerve leaves the eyeball is the optic disc, where the absence of receptors causes the blind spot (which is discussed on the website in **A Step Further: The Blind Spot**).

The vertebrate eye acts in some ways like a camera

Vision depends on many different structures and processes. First among these are the structures and processes that enable the eye to form relatively accurate optical images on the retina. Accurate optical images are a prerequisite for discerning the shapes of objects; that is, light from a point on a target object must end up as a point—rather than a blur—in the retinal image. Without optical images, light-sensitive cells would be able to detect only the presence or absence of light and would not be able to see forms, just as a camera without a lens could not produce a picture.

To produce optical images, the eye has many of the features of a camera, starting with the **cornea** and **lens** to focus light (**Figure 10.7**). Light travels in a straight line until it encounters a change in the density of the medium, which causes light rays to bend. This bending of light rays, called **refraction**, is the basis of such instruments as eyeglasses, telescopes, and microscopes. The cornea of the eye—the curvature of which is fixed—bends light rays and is primarily responsible for forming the image on the retina.

In a camera, the lens moves nearer to or farther from the film to adjust focus, and the same system is used in the eyes of fishes, amphibians, and reptiles. In mammals and birds, however, focus is adjusted by changes in the *shape* of the lens, which is controlled by the **ciliary muscles** inside the eye. As the degree of contraction of the ciliary muscles varies, the lens focuses images of nearer or farther objects so that they form sharp images on the retina; this process of focusing is called **accommodation**.

In many people the eyeball is either too long or too short to allow the lens to bring images into sharp focus on the retina. Eyeglasses or contact lenses can correct such conditions. Near the end of this chapter we'll see that preventive steps can be taken during childhood to avoid overlengthening of the eyeball. As mammals age, their lenses become less elastic and therefore less able to change curvature to bring nearby objects into focus. Aging humans correct this problem by wearing reading glasses.

The amount of light that enters the eye is controlled by the size of the **pupil**, which is an opening in the colorful disc called the **iris** (see Figure 10.7). In Chapter 2 we mentioned that dilation of the pupils is controlled by the sympathetic division of the autonomic system, and constriction, by the parasympathetic division. Because usually both divisions are active, pupil size reflects a balance of influences.

During an eye examination, the doctor may use a drug to block acetylcholine transmission in the parasympathetic synapses of your iris; this drug relaxes the sphincter muscle fibers and permits the pupil to open widely. One drug that has this effect—*belladonna* (Italian for "beautiful lady")—got its name because it was thought to make a woman more beautiful by giving her the wide-open pupils of an attentive person. Other drugs, such as morphine, constrict the pupils.

cornea The transparent outer layer of the eye, whose curvature is fixed. It bends light rays and is primarily responsible for forming the image on the retina.

lens A structure in the eye that helps focus an image on the retina.

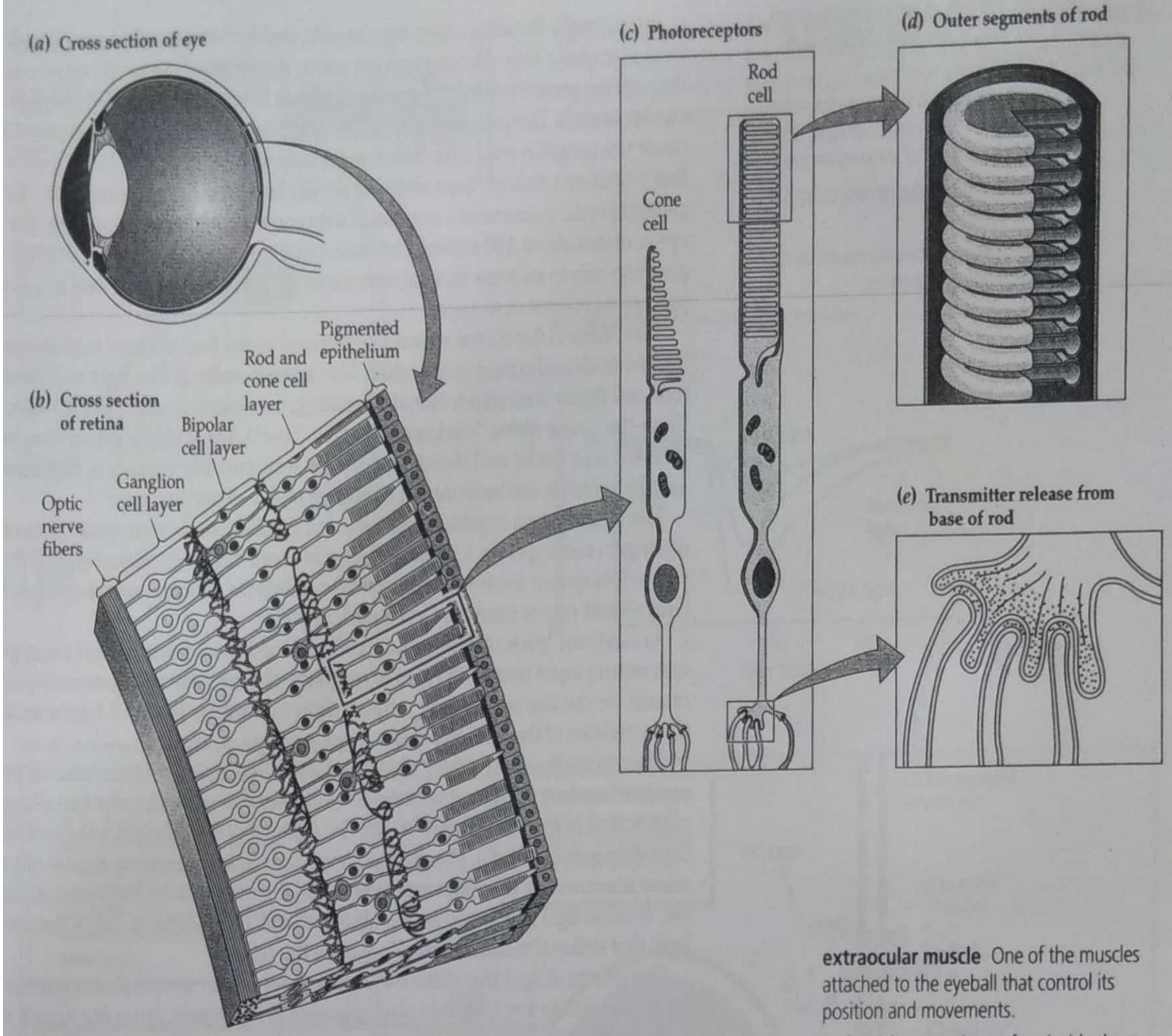
refraction The bending of light rays by a change in the density of a medium, such as the cornea and the lens of the eyes.

ciliary muscle One of the muscles that controls the shape of the lens inside the eye, focusing an image on the retina.

accommodation The process of focusing by the ciliary muscles and the lens to form a sharp image on the retina.

pupil The aperture, formed by the iris, that allows light to enter the eye.

iris The circular structure of the eye that provides an opening to form the pupil.



10.8 Anatomy of the Retina (a) This cross section of an eye shows the location of the retina. (b) A cross section of the retina shows its layered structure. (c–e) Rods and cones differ from each other in structure.

The movement of the eyes is controlled by the **extraocular muscles**, three pairs of muscles that extend from the outside of the eyeball to the bony socket of the eye. Fixating still or moving targets requires delicate control of these muscles.

Visual processing begins in the retina

The first stages of visual-information processing occur in the **retina**, the receptive surface inside the back of the eye (**Figure 10.8*a***). The retina is only 200 to 300 μm thick—not much thicker than the edge of a razor blade—but it contains several types of cells in distinct layers (**Figure 10.8*b***). The photoreceptor cells are modified neurons; some are called **rods** because of their relatively long, narrow form; others are called **cones** (**Figure 10.8*c***). The rods and cones release neurotransmitter molecules that control the activity of the **bipolar cells** that synapse with them (see Figure 10.8*b*). The bipolar cells, in turn, connect with **ganglion cells**. The axons of the ganglion cells form the **optic nerve**, which carries information to the brain.

Horizontal cells and **amacrine cells** are especially significant in interactions within the retina, such as lateral inhibition. The horizontal cells make contacts among the receptor cells and bipolar cells; the amacrine cells contact both the bipolar and the ganglion cells.

extraocular muscle One of the muscles attached to the eyeball that control its position and movements.

retina The receptive surface inside the eye that contains photoreceptors and other neurons.

rod A class of light-sensitive receptor cells (photoreceptors) in the retina that are most active at low levels of light.

cone A class of photoreceptor cells in the retina that are responsible for color vision.

bipolar cells A class of interneurons of the retina that receive information from rods and cones and pass the information to retinal ganglion cells.

ganglion cells A class of cells in the retina whose axons form the optic nerve.

optic nerve Cranial nerve II; the collection of ganglion cell axons that extend from the retina to the optic chiasm.

horizontal cells Specialized retinal cells that contact both the receptor cells and the bipolar cells.

amacrine cells Specialized retinal cells that contact both the bipolar cells and the ganglion cells, and are especially significant in inhibitory interactions within the retina.

scotopic system A system in the retina that operates at low levels of light and involves the rods.

photopic system A system in the retina that operates at high levels of light, shows sensitivity to color, and involves the cones.

rhodopsin The photopigment in rods that responds to light.

RETINAL One of the two components of photopigments in the retina.

Interestingly, the rods, cones, bipolar cells, and horizontal cells generate only graded local potentials; they do not generate action potentials. These cells affect each other through the graded release of neurotransmitters in response to graded changes in electrical potentials. The ganglion cells, on the other hand, do conduct action potentials. Because the ganglion cells have action potentials and are relatively large, they were the first retinal cells to have their electrical activity recorded. From the receptor cells to the ganglion cells, an enormous number of data converge and are compressed; the human eye contains about 100 million rods and 4 million cones, but there are only 1 million ganglion cells to transmit that information to the brain. Thus a great deal of information processing is done in the eye.

Two different functional systems correspond to the two different populations of receptors (rods and cones) in the retina. One system works in dim light and involves the rods and highly convergent neural processing; this system is called the **scotopic system** (from the Greek *skotos*, "darkness," and *ops*, "eye"). The scotopic system has only one receptor type (rods) and therefore does not respond differentially to different wavelengths, which is the basis for the saying "at night, all cats are gray."

The other system requires more light and involves much more detailed neural processing; in some species, it shows differential sensitivity to wavelengths, enabling color vision. This system involves the cones and is called the **photopic system** (which, like the term *photon*, comes from the Greek *phos*, "light").

At moderate levels of illumination, both rods and cones function, and some ganglion cells receive input from both types of receptors. Having these two systems is part of the reason we can see over a wide range of light intensities. **Table 10.1** summarizes the characteristics of the photopic and scotopic systems.

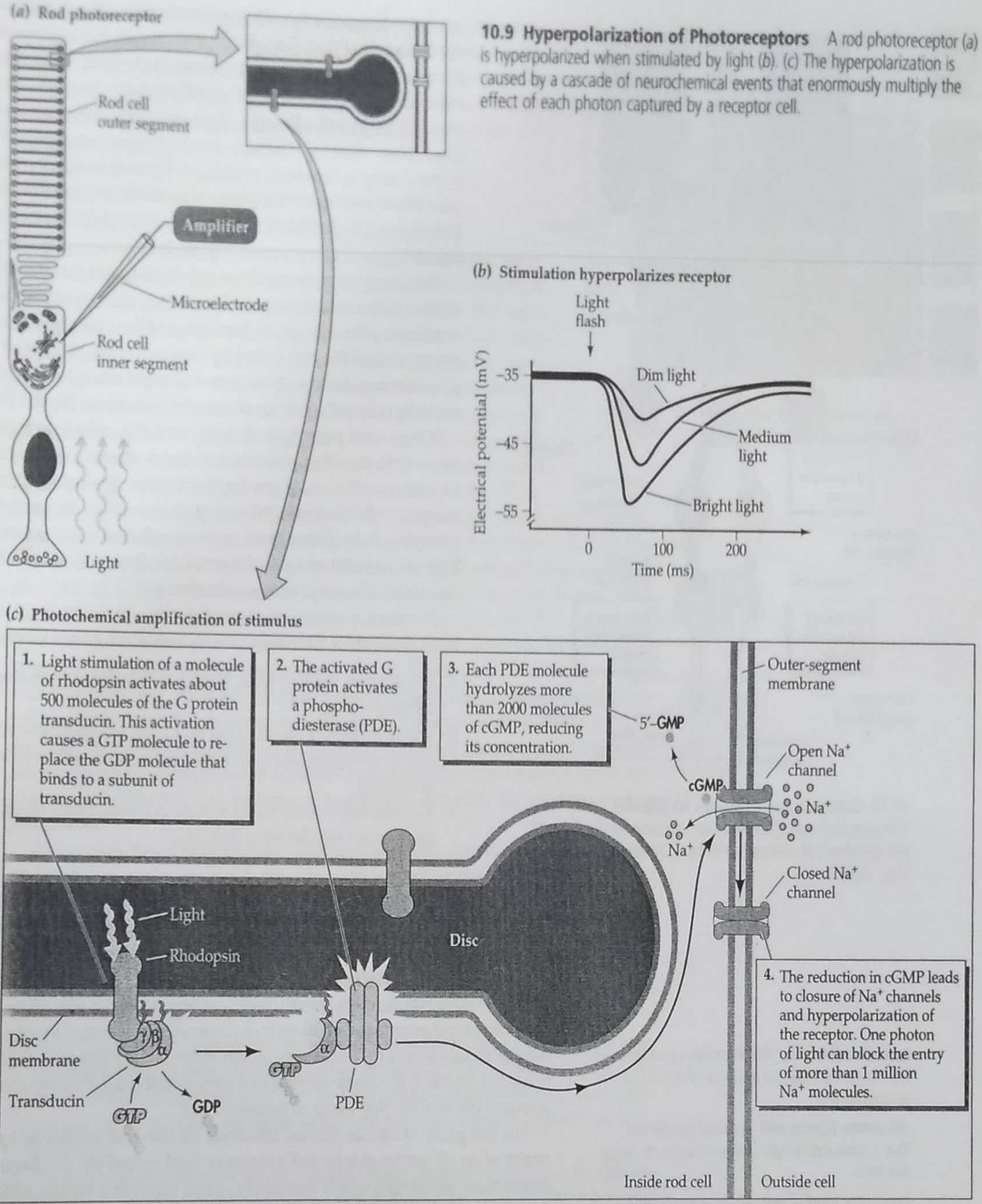
The extraordinary sensitivity of rods and cones is the result of their unusual structure and biochemistry. A portion of their structure, when magnified, looks like a large stack of pancakes or discs (see Figure 10.8*d*). The stacking of discs increases the probability of capturing quanta of light, an especially important function because light is reflected in many directions by the surface of the eyeball, the lens, and the fluid media inside the eye. Because light is reflected and/or absorbed at all these surfaces, only a fraction of the light that strikes the cornea actually reaches the retina.

The quanta of light that strike the discs are captured by special photopigment receptor molecules. In the rods this photopigment is **rhodopsin** (from the Greek *rhodon*, "rose," and *opsis*, "vision"). Cones use similar photopigments, as we will see later. The rod and cone photopigments in the eye consist of two parts: **RETINAL** (an abbreviated

TABLE 10.1 Properties of the Human Photopic and Scotopic Visual Systems

Property	Photopic system	Scotopic system
Receptors[a]	Cones	Rods
Approximate number of receptors per eye	4 million	100 million
Photopigments[b]	Three classes of cone opsins; the basis of color vision	Rhodopsin
Sensitivity	Low; needs relatively strong stimulation; used for day vision	High; can be stimulated by weak light intensity; used for night vision
Location in retina[c]	Concentrated in and near fovea; present less densely throughout retina	Outside fovea
Receptive field size and visual acuity	Small in fovea, so acuity is high; larger outside fovea	Larger, so acuity is lower
Temporal responses	Relatively rapid	Slow

[a] Cones and rods are illustrated in Figure 10.8c.
[b] Figure 10.24 shows the spectral sensitivities of the photopigments.
[c] See Figure 10.12.


(a) Rod photoreceptor
Rod cell outer segment
Amplifier
Microelectrode
Rod cell inner segment
Light
(b) Stimulation hyperpolarizes receptor
Light flash
Electrical potential (mV)
–35
–45
–55
Dim light
Medium light
Bright light
0
100
200
Time (ms)
(c) Photochemical amplification of stimulus
1. Light stimulation of a molecule of rhodopsin activates about 500 molecules of the G protein transducin. This activation causes a GTP molecule to replace the GDP molecule that binds to a subunit of transducin.
2. The activated G protein activates a phosphodiesterase (PDE).
3. Each PDE molecule hydrolyzes more than 2000 molecules of cGMP, reducing its concentration.
Outer-segment membrane
5′-GMP
cGMP
Open Na⁺ channel
Na⁺
Na⁺
Closed Na⁺ channel
Light
Rhodopsin
Disc
γ
β
α
α
Disc membrane
Transducin
GTP
GDP
GTP
PDE
4. The reduction in cGMP leads to closure of Na⁺ channels and hyperpolarization of the receptor. One photon of light can block the entry of more than 1 million Na⁺ molecules.
Inside rod cell
Outside cell

10.9 Hyperpolarization of Photoreceptors A rod photoreceptor (*a*) is hyperpolarized when stimulated by light (*b*). (*c*) The hyperpolarization is caused by a cascade of neurochemical events that enormously multiply the effect of each photon captured by a receptor cell.

name for *retinaldehyde,* which is vitamin A aldehyde) and **opsin**. (In this book the noun RETINAL, standing for the molecule, is printed in small capital letters to distinguish it from the adjective *retinal,* meaning "pertaining to the retina.") The visual receptor molecules span the membranes of receptor discs and have structures that are similar to those of the G protein–coupled neurotransmitter receptors that we discussed in Chapter 3.

When light activates a rhodopsin molecule (**Figure 10.9**), the RETINAL dissociates rapidly from the opsin, revealing an enzymatic site on the opsin molecule. The activated

opsin One of the two components of photopigments in the retina.

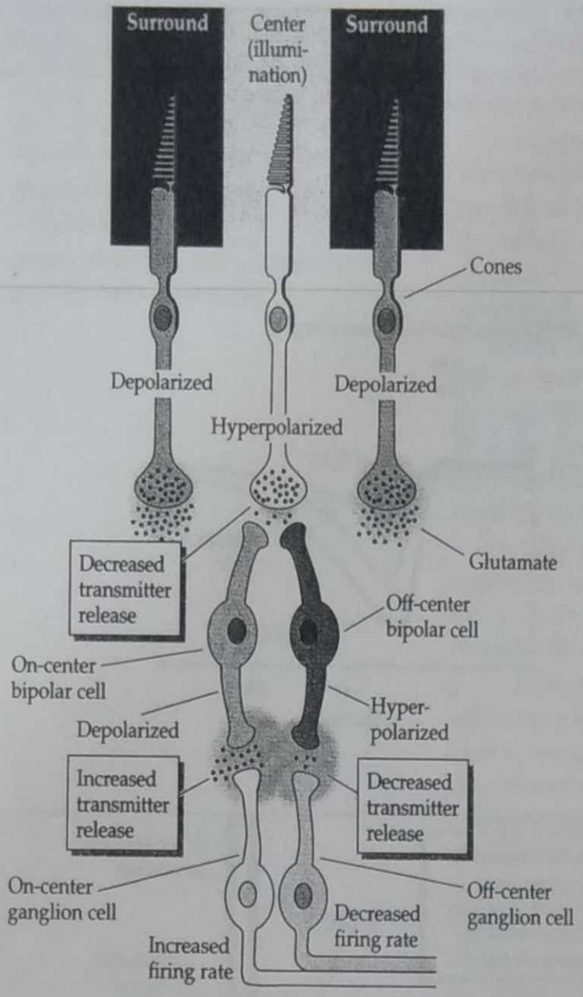
opsin combines rapidly with many molecules of the G protein transducin (**Figure 10.9*c***). Transducin in turn acts through an enzyme, phosphodiesterase (PDE), to transform cyclic GMP (cyclic guanosine monophosphate) to 5′-GMP. Cyclic GMP holds channels for sodium ions (Na^+) open; stimulation by light initiates a cascade of events that closes these channels. Capture of a single quantum of light can lead to the closing of hundreds of sodium channels in the photoreceptor membrane and block the entry of more than a million Na^+ ions (Schnapf and Baylor, 1987). Closing the Na^+ channels creates a hyperpolarizing generator potential (**Figure 10.9*b***).

This change of potential represents the initial electrical signal of activation of the visual pathway. Stimulation of rhodopsin by light hyperpolarizes the rods, just as stimulation of the cone pigments by light hyperpolarizes the cones. And for rods and cones, the size of the hyperpolarizing photoreceptor potential determines the magnitude of the reduction in the release of synaptic transmitter (Figure 10.8*e*).

It may seem puzzling at first that stimulation by light *hyper*polarizes vertebrate retinal photoreceptors and causes them to release *less* neurotransmitter, since sensory stimulation depolarizes most other receptor cells. But remember that the visual system responds to *changes* in light. Either an increase or a decrease in the intensity of light can stimulate the visual system, and hyperpolarization is just as much a neural signal as depolarization is.

The cascade of processes required to stimulate the visual receptors helps account for three major characteristics of the visual system:

1. Its *sensitivity*, because weak stimuli are amplified to produce physiological effects
2. The *integration* of the stimulus over time, which makes vision relatively slow (compared, for example, to audition) but increases its sensitivity
3. The *adaptation* of the visual system to a wide range of light intensities, as we will discuss a little later



10.10 Connections of Cones to Bipolar Cells
Stimulation of one photoreceptor may increase the firing of one ganglion cell and reduce firing of another. (After Purves et al., 2001.)

Photoreceptors excite some retinal cells and inhibit others

At their resting potentials, both rod and cone photoreceptors steadily release the synaptic neurotransmitter glutamate. Light always hyperpolarizes the photoreceptors, causing them to release less glutamate. But the response of the bipolar cells that receive this glutamate differs depending on what type of glutamate receptor they possess. Glutamate depolarizes one group of bipolar cells but hyperpolarizes another group. These groups differ in their receptive fields. As we noted in Chapter 8, the **receptive field** of a sensory cell consists of the stimulus region and the features that excite or inhibit the cell.

The first group of bipolar cells are **off-center bipolar cells**: turning *off* light in the center of an off-center bipolar cell's receptive field excites the cell because it receives more glutamate, which depolarizes these off-center bipolar cells (**Figure 10.10**). The second group are **on-center bipolar cells**: turning *on* a light in the center of an on-center bipolar cell's receptive field excites these bipolar cells because they receive less glutamate, which otherwise inhibits the on-center bipolar cell.

Bipolar cells also release glutamate, but glutamate always depolarizes the ganglion cells. Therefore, when light is turned on, on-center bipolar cells depolarize (excite) **on-center ganglion cells**; and when light is turned off, off-center bipolar cells depolarize (excite) **off-center ganglion cells** (see Figure 10.10). The stimulated on-center and off-center ganglion cells then fire nerve impulses and report "light" or "dark" to higher visual centers. There are different types of ganglion cells, which we will describe shortly.

receptive field The stimulus region and features that cause the maximal response of a cell in a sensory system.

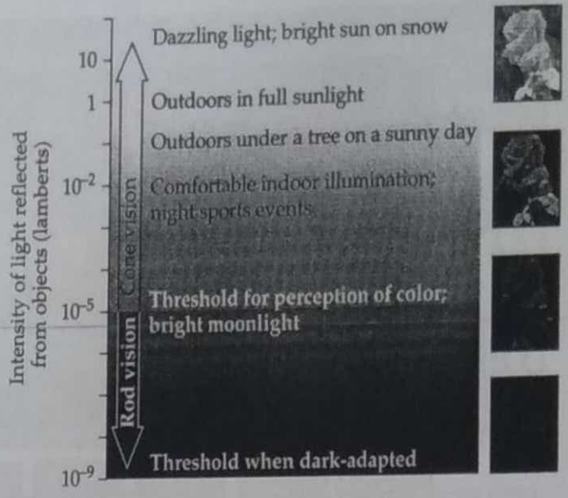
off-center bipolar cell A retinal bipolar cell that is inhibited by light in the center of its receptive field.

on-center bipolar cell A retinal bipolar cell that is excited by light in the center of its receptive field.

on-center ganglion cell A retinal ganglion cell that is activated when light is presented to the center, rather than the periphery, of the cell's receptive field.

off-center ganglion cell A retinal ganglion cell that is activated when light is presented to the periphery, rather than the center, of the cell's receptive field.

A stimulus in a particular part of the visual field affects only those visual cells whose receptive fields are in the corresponding part of the retina. This situation is similar to what occurs in the somatosensory system, where cells with different somatosensory receptive fields serve different parts of the body surface (see Figure 8.12) and the ensemble covers the whole body.



10.11 The Wide Range of Sensitivity to Light Intensity

Different mechanisms enable the eyes to work over a wide range of light intensities

Many sensory systems have to work over wide ranges of stimulus intensity, as we learned in Chapter 8. This is certainly true of the visual system: a very bright light is about 10 billion times as intense as the weakest lights that we can see. At any given time, however, we can discriminate over only a small fraction of this range of light intensity. Let's discuss the mechanisms by which the eye adapts to the prevailing level of illumination.

One way the visual system deals with a large range of intensities is by adjusting the size of the pupil. In bright light the pupil contracts quickly to admit only about one-sixteenth as much light as when illumination is dim. Although rapid, this pupil response cannot account for the billion-fold range of visual sensitivity (**Figure 10.11**). Another mechanism for handling different light intensities is **range fractionation**; that is, different receptors—some with low thresholds (rods) and others with high thresholds (cones) handle different intensities (see Table 10.1). Figure 8.6 illustrated range fractionation for the somatosensory system.

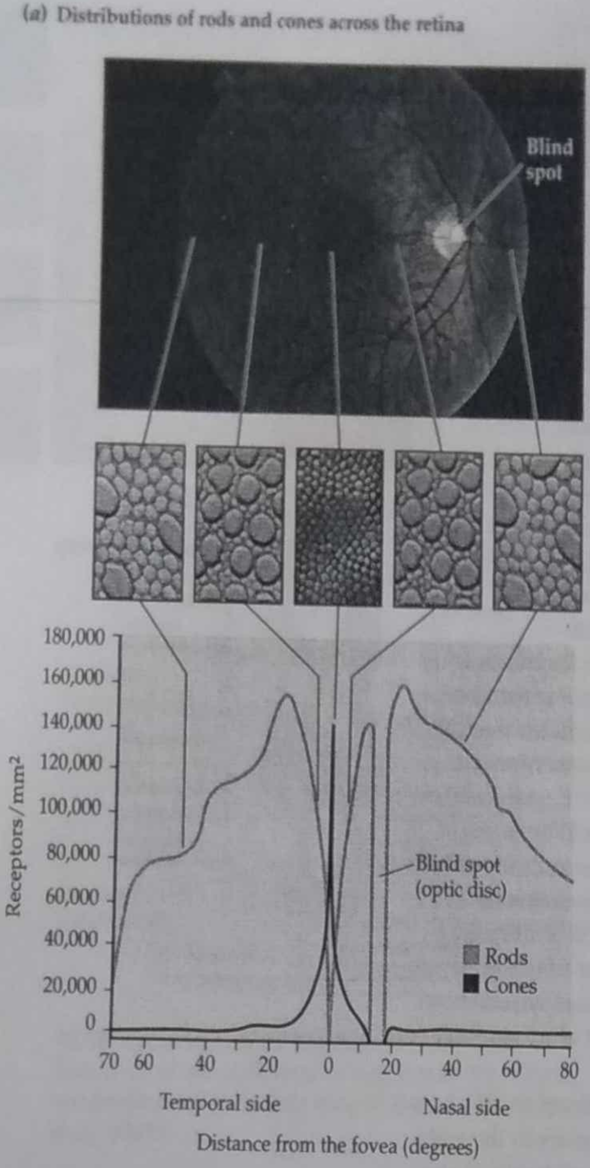
Additional range fractionation would carry an unacceptable cost: If, at a particular light level, several sets of receptors were not responding, acuity would be impaired. If only a fraction of the receptors responded to the small changes in the intensity of light around a given level, the active receptors would be spaced apart from each other in the retina, and the "grain" of the retina would be coarse. The eye solves this problem by giving photoreceptors a great range of adaptation; that is, each receptor adjusts its sensitivity to match the average level of ambient illumination. Thus the visual system is concerned with differences, or changes, in brightness—not with the absolute level of illumination.

At any given time a photoreceptor operates over a range of intensities of about a hundredfold; that is, it is completely depolarized by a stimulus about one-tenth the ambient level of illumination, and a light ten times as intense as the ambient level will completely hyperpolarize it. The receptors constantly shift their whole range of response to work around the prevailing level of illumination. Further adaptation occurs in the ganglion cells and the lateral geniculate nucleus, and probably at higher levels too.

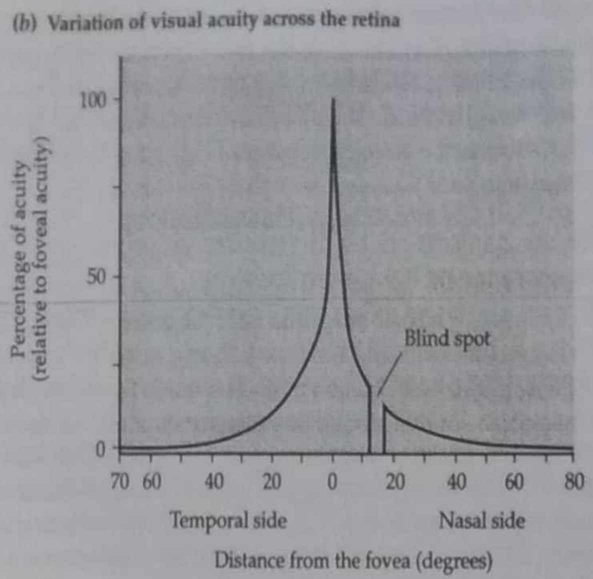
Three main factors help account for receptor adaptation in the visual system:

1. *The role of calcium.* Probably the most important factor is one shared by other sensory modalities: varying the concentration of calcium (Ca^{2+}) ions (E. N. Pugh and Lamb, 1990). When intracellular Ca^{2+} ions are bound experimentally and thus made unavailable for reactions, the visual system can no longer adapt to higher levels of illumination.
2. *The level of photopigment.* When the photoreceptor pigment is split apart by light, its two components—RETINAL and opsin—slowly recombine, so the balance between the rate of breakdown of the pigment and its rate of recombination determines how much photopigment is available at any given time to respond to stimulation by light. If you go from bright daylight into a dark theater, it takes several minutes until enough rhodopsin becomes available to restore your dark vision.
3. *The availability of retinal chemicals for transduction.* Several retinal chemicals are required for transduction. They tend to be abundant at low levels of illumination but increasingly rare at higher levels of illumination, so increasing numbers of photons are required to activate them and hyperpolarize the receptors (E. N. Pugh and Lamb, 1993).

range fractionation A hypothesis of stimulus intensity perception stating that a wide range of intensity values can be encoded by a group of cells, each of which is a specialist for a particular range of stimulus intensities.



(a) Distributions of rods and cones across the retina



(b) Variation of visual acuity across the retina

10.12 Densities of Retinal Receptors and Visual Acuity
(*a*) The photograph of the retina was taken through the pupil. The graph shows that rods and cones vary in size and distribution across the retina. (*b*) The variation of visual acuity across the retina reflects the distribution of cones.

Acuity is best in foveal vision because of the dense array of cones in the fovea

Early in this chapter we noted that acuity is especially fine in the center of the visual field and falls off rapidly toward the periphery. Reasons for this difference have been found in the retina and successive levels of the visual system, each of which is a detailed map of the visible world. Although the neural maps preserve the order of the visual field, each map is topographic; that is, it enlarges some regions at the expense of others.

Figure 10.12*a* shows a photograph of the back of the eye seen through the pupil. The central region, called the **fovea** (Latin for "pit"), has a dense concentration of cones, and in this region light reaches the cones without having to pass through other layers of cells and blood vessels (**Figure 10.13**). The **optic disc**, to the nasal side of the fovea, is where blood vessels enter and leave the eye. There are no photoreceptors at the optic disc, so there is a **blind spot** here. To locate your blind spot and experience firsthand some of its interesting features, see **A Step Further: The Blind Spot** on the website.

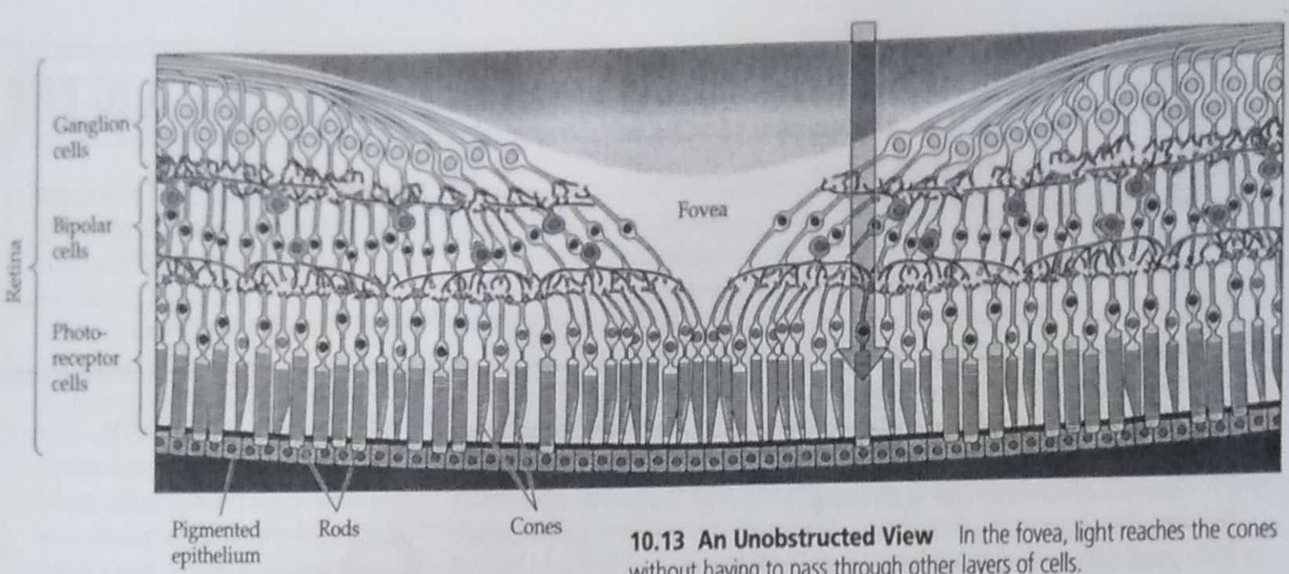
The high concentration of cones in the fovea accounts for high visual acuity in this region (**Figure 10.12*b***). People differ in their concentrations of cones (Curcio et al., 1987), and this variation may be related to individual differences in visual acuity. Species differences in visual acuity also reflect the density of cones in the fovea. For example, hawks, whose acuity is much greater than that of humans, have much narrower and more densely packed cones in the fovea than humans do. In the human retina, both cones and rods are wider toward the periphery.

The rods show a different distribution from the cones: they are absent in the fovea but more numerous than cones in the periphery of the retina (see Figure 10.12*a*). They are the most concentrated in a ring about 20° away from the center of the retina. This is why, if you want to see a dim star, you do best to search for it a little off to the side of your center of gaze. Not only are the rods more sensitive to dim light than the cones, but input from more rods converges on ganglion cells in the scotopic system, further increasing its sensitivity to weak stimuli.

fovea The central portion of the retina, packed with the most photoreceptors and therefore the center of our gaze.

optic disc The region of the retina devoid of receptor cells because ganglion cell axons and blood vessels exit the eyeball there.

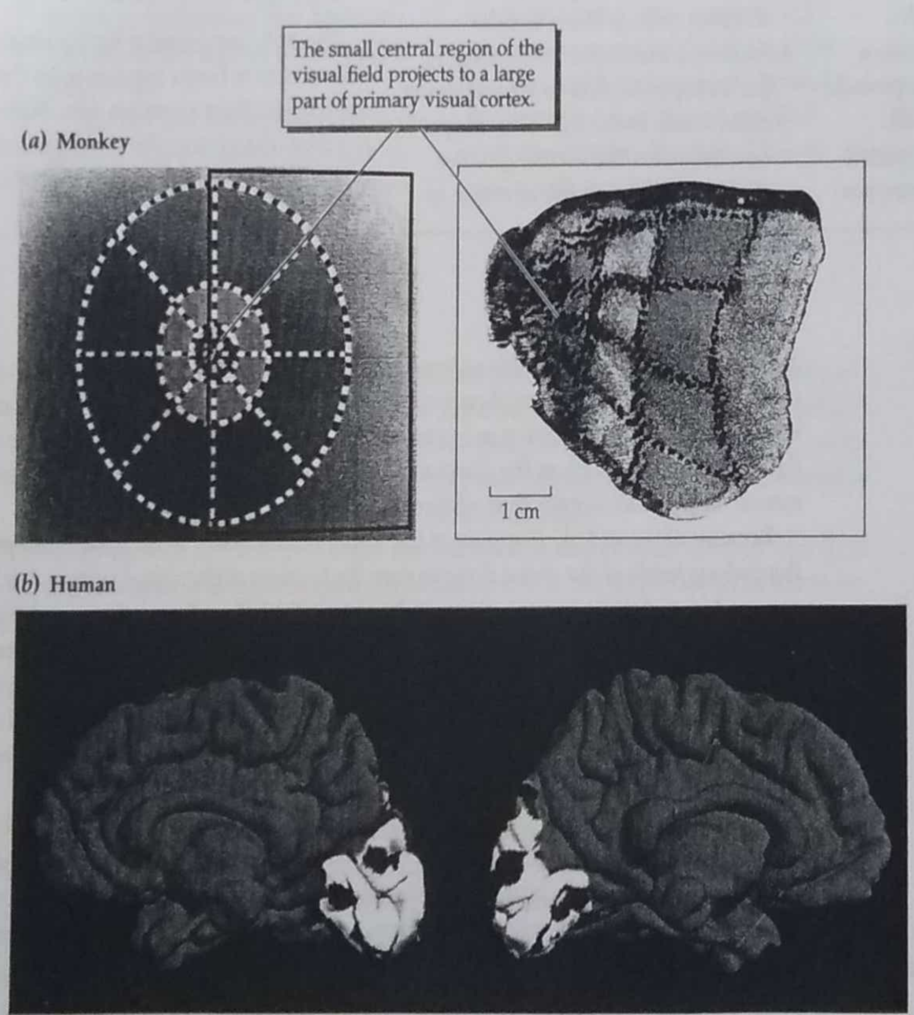
blind spot The place through which blood vessels enter the retina. Because there are no receptors in this region, light striking it cannot be seen.


Retina
Ganglion cells
Bipolar cells
Photo-receptor cells
Fovea
Pigmented epithelium
Rods
Cones

10.13 An Unobstructed View In the fovea, light reaches the cones without having to pass through other layers of cells.

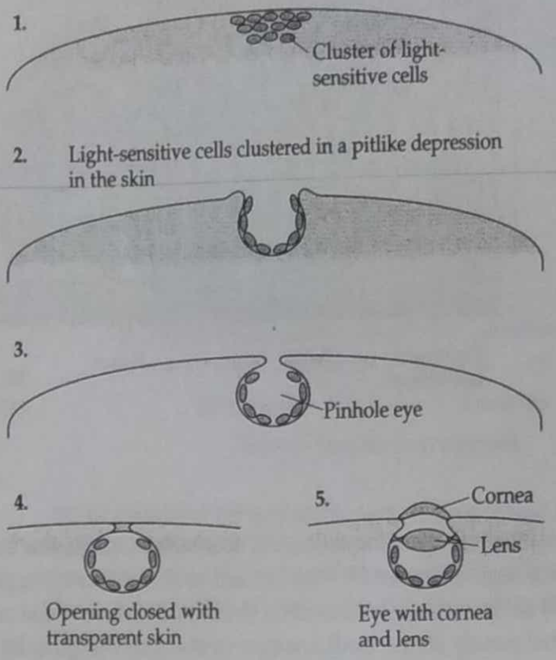
A major part of the projection of visual space onto topographic brain maps is devoted to the foveal region (**Figure 10.14*a***) (Tootell et al., 1982). Although the **primary visual cortex (V1)** of the monkey is located on the lateral surface of the occipital area, human V1 is located mainly on the medial surface of the cortex (**Figure 10.14*b***; see also Figure 10.19*d*). The fact that, as in the monkey, about half of the human V1 is devoted to the fovea and the retinal region just around the fovea does not mean that our spatial per-

primary visual cortex (V1) Also called *striate cortex* or *area 17*. The region of the occipital cortex where most visual information first arrives.


The small central region of the visual field projects to a large part of primary visual cortex.
(a) Monkey
1 cm
(b) Human

10.14 Location of the Primary Visual Cortex (a) A pattern of flickering lights (*left*) was shown in a monkey's visual field, and a map of the visual field was revealed by autoradiography in a flattened section of the primary visual cortex (*right*). (*b*) Maps of human visual cortex derived from functional-MRI measurements show primary visual cortex as the innermost yellow band on each medial view. (Part a from Tootell et al., 1988; *b* from Tootell et al., 1998; both courtesy of Roger Tootell.)

BOX 10.2 Eyes with Lenses Have Evolved in Several Phyla


1.
Cluster of light-sensitive cells
2. Light-sensitive cells clustered in a pitlike depression in the skin
3.
Pinhole eye
4.
Opening closed with transparent skin
5.
Cornea
Lens
Eye with cornea and lens

Phylogenetic studies indicate that the evolution of eyes with lenses, like those of a mammal or an octopus, included the following steps (Fernald, 2000):

1. *Concentrating light-sensitive cells* into localized groups that serve as photoreceptor organs. Animals with such photoreceptor organs have better chances of surviving and reproducing than do similar animals with scattered receptor cells, because photoreceptor organs facilitate an ability to respond differently to stimuli that strike different parts of the body surface.
2. *Clustering light receptors* at the bottom of pitlike or cuplike depressions in the skin. Animals with this adaptation can discriminate better among stimuli that come from different directions. They also perceive increased contrast of stimuli against a background of ambient light.
3. *Narrowing the top of the cup* into a small aperture so that, like a pinhole camera, the eye can focus well.
4. *Closing the opening with transparent skin or filling the cup with a transparent substance.* This covering protects the eye against the entry of foreign substances that might injure the receptor cells or block vision.
5. *Forming a lens* either by thickening the transparent skin or by modifying other tissue in the eye. This adaptation improves the focusing of the eye while allowing the aperture to be relatively large to let in more light; thus, vision can be acute even when light is not intense.

The only requirement for the evolution of eyes to begin appears to be the existence of light-sensitive cells. Natural selection then favors the development of auxiliary mechanisms to improve vi-

ception is distorted. Rather, this representation makes possible the great acuity of spatial discrimination in the central part of the visual field. Our acuity falls off about as rapidly in the horizontal direction as in the vertical direction, but species that live in open, flat environments (such as the cheetah and the rabbit) have fields of acute vision that extend farther horizontally than vertically.

Because of the orderly mapping of the visual field (known as *retinotopic mapping*) at the various levels of the visual system, damage to parts of the visual system can be diagnosed from defects in perception of the visual field. If we know the site of injury in the visual pathway, we can predict the location of such a perceptual gap, or **scotoma** (plural *scotomas* or *scotomata*), in the visual field. Although the word *scotoma* comes from the Greek *skotos*, meaning "darkness," a scotoma is not perceived as a dark patch in the visual field; rather it is a spot where nothing can be perceived, and usually rigorous testing is required to demonstrate its existence.

Within a scotoma, a person cannot consciously perceive visual cues, but some visual discrimination in this region may still be possible; this paradoxical phenomenon has been called *blindsight*. In other cases, stimuli that cannot be seen within a scotoma affect judgments of stimuli outside it (Stoerig and Cowey, 1997). Blindsight may also be related to the phenomenon of *hemispatial neglect*—neglect of the side opposite to an injured cerebral hemisphere—which we will discuss in Chapter 19.

scotoma A region of blindness caused by injury to the visual pathway or brain.

BOX 10.2 (continued)

sion. Many kinds of cells show some sensitivity to light, and different phyla have modified different types of cells for specialized photoreceptors. The most common starting point has been cells of epidermal (skin) origin, but some lines (including that of our chordate vertebrate ancestors) derived their visual receptors from cells of neural origin. All known visual systems use a light-receptor molecule similar to rhodopsin, indicating a basic similarity among them.

Phylogenetic studies of the structure and development of eyes led investigators to conclude that eyes evolved independently in many different phyla (Salvini-Plawen and Mayr, 1977). A competent optical system with a lens, however, has evolved in only 6 of the 33 phyla of multicellular animals. These few phyla have been very successful; they account for about 96% of known species of multicellular animals. An effective optical system may have contributed to this success (Land and Fernald, 1992).

The fact that the cephalopods (such as squid and octopuses) evolved a visual system that in many ways resembles that of vertebrates (from fishes to humans) suggests that there are major constraints on the development of a visual system for a large, rapidly moving animal. Let's look at some of the main similarities and differences between the eyes of cephalopods and vertebrates. In both, the eyes are relatively large, allowing for many receptors and the ability to gather large amounts of light. The incoming light is regulated by a pupil and focused by a lens. In both cephalopods and vertebrates, three sets of extraocular muscles move the eyeballs.

An important difference in eye structure between cephalopods and vertebrates is the organization of the retina. In the vertebrate eye, light must travel through neurons and blood vessels to reach the receptors, and the area where the neural axons and blood vessels enter and leave the retina forms the blind spot. In cephalopods the organization is more efficient in some respects: light reaches the receptors directly, and the neurons and blood vessels lie behind the receptors; thus there is no blind spot. The detailed structure of the receptor cells is quite different in cephalopods and vertebrates. In addition, the visual stimulus causes depolarization of cephalopod (and most invertebrate) retinal receptor cells, but it causes hyperpolarization of fish and mammalian retinal photoreceptors.

It is still uncertain whether eyes of all species evolved from a single progenitor or have arisen more than once during evolution (Fernald, 2000). The major similarities between cephalopod and vertebrate eyes have often been cited as examples of convergent evolution, showing ways in which similar functions can be achieved with different structures and processes, starting from different origins. However, the eyes of all seeing animals share at least two important genetic features: First, they all use opsin pigments. Second, the compound eye of the fruit fly *Drosophila*, the vertebrate eye, and the cephalopod eye all develop through genes of the *Pax* family. The finding that highly homologous molecules are key regulators of eye development in different phyla argues that eyes in all phyla share a common origin.

Before ending our discussion of the retina, we should mention that some retinal ganglion cells possess a special photopigment that makes them sensitive to light (Hattar et al., 2002). As we will see in Chapter 14, these ganglion cells help control daily cycles of behavior called *circadian rhythms*, and they also inform the brain about the level of ambient light to control pupil diameter (Lucas et al., 2003).

When we look at a complex organ like the eye of a mammal, an octopus, or a fly, it is hard at first to understand how it could have evolved. But inspection of different living species reveals a gradation from very simple light-sensitive cells to increasingly complex organs with focusing devices (**Box 10.2**), and each kind of photoreceptor confers benefits on the animal that possesses it.

Neural Signals Travel from the Retina to Several Brain Regions

The signals that result from visual processing in the retina converge on the ganglion cells, from which they then diverge to several brain structures (see Figure 3.15*b*). The ganglion cells in each eye produce action potentials that are conducted along their axons to send visual information to the brain (see Figure 10.6). These axons make up the optic nerves (also known as cranial nerve II). In all vertebrates, some or all of the axons of each optic nerve cross to the opposite cerebral hemisphere.

The optic nerves cross the midline at the **optic chiasm** (named for the Greek letter X [*chi*] because of its crossover shape), which is located just anterior to the stalk of the pituitary gland. In humans, axons from the half of the retina toward the nose (the *nasal retina*) cross over to the opposite side of the brain. The half of the retina toward the side of the head (the *temporal retina*) projects its axons to its own side of the head. After they pass the optic chiasm, the axons of the retinal ganglion cells are known collectively as the **optic tract**. Proportionally more axons cross the midline in animals, such as rodents, that have laterally placed eyes with little binocular overlap in their fields of vision.

Most axons of the optic tract terminate on cells in the **lateral geniculate nucleus (LGN)**, which is the visual part of the thalamus. Axons of postsynaptic cells in the LGN form the **optic radiations**, which terminate in the visual areas of the **occipital cortex** at the back of the brain. The primary visual cortex is often called the **striate cortex** because a broad stripe, or *striation*, is visible in anatomical sections through this region; the stripe represents layer IV of the cortex, where the optic-radiation fibers arrive. Inputs from the two eyes converge on cells beyond layer IV of the primary visual cortex, making binocular (three-dimensional) vision possible.

In addition to the primary visual cortex (V1) shown in Figures 10.6 and 10.14, numerous surrounding regions of the cortex are also largely visual in function (see Figure 10.19*c*). Visual cortical areas outside the striate cortex are sometimes called **extrastriate cortex**. As Figure 10.6 shows, the visual cortex in the right cerebral hemisphere receives its input from the left half of the visual field, and the visual cortex in the left hemisphere receives its input from the right half of the visual field. Figure 10.6 shows that some retinal ganglion cells send their optic-tract axons to the superior colliculus in the midbrain. The superior colliculus helps coordinate rapid movements of the eyes toward a target.

Investigators have found several cortical areas for each sensory modality, and most of these areas are laid out in an orderly topographic map of the receptor surface (C. N. Woolsey, 1981a, 1981b, 1981c). Examination of the cortex of the macaque reveals more than 30 visual areas, many of which contain a topographic representation of the retina (see Figure 10.19*c*). The different cortical regions work in parallel to process different aspects of visual perception, such as form, color, location, and movement, as we will discuss later in this chapter.

Neurons at Different Levels of the Visual System Have Very Different Receptive Fields

The nature of the receptive field of a cell gives us good clues about its function(s) in perception. Cells in the retina or LGN can be activated by simple spots of light, but many cells in the visual cortex are more demanding and respond only to more-complicated stimuli. In the next sections we will see that neurons at lower levels in the visual system seem to account for some perceptual phenomena and neurons at higher levels in the visual system account for others.

Neurons in the retina and the LGN have concentric receptive fields

Two scientists discovered the main features of the receptive fields of vertebrate retinal ganglion cells independently within a few months of each other: Stephen Kuffler (1913–1980), studying the cat (Kuffler, 1953); and Horace Barlow, studying the frog (Barlow, 1953). They recorded from single ganglion cells while they moved a small spot of light across the visual field, keeping the animal's eye still. Results showed that the receptive fields of retinal ganglion cells are concentric, consisting of a roughly circular central area and a ring around it.

Both bipolar cells and ganglion cells have two basic types of retinal receptive fields: **on-center/off-surround** (**Figure 10.15*a***) and **off-center/on-surround** (**Figure 10.15*b***). The center and its surround are always antagonistic. These antagonistic effects explain why uniform illumination of the visual field is less effective in activating a ganglion cell than is a well-placed small spot or a line or edge passing through the center of the cell's receptive field.

optic chiasm The point at which the two optic nerves meet.

optic tract The axons of retinal ganglion cells after they have passed the optic chiasm; most terminate in the lateral geniculate nucleus.

lateral geniculate nucleus (LGN) The part of the thalamus that receives information from the optic tract and sends it to visual areas in the occipital cortex.

optic radiation Axons from the lateral geniculate nucleus that terminate in the primary visual areas of the occipital cortex.

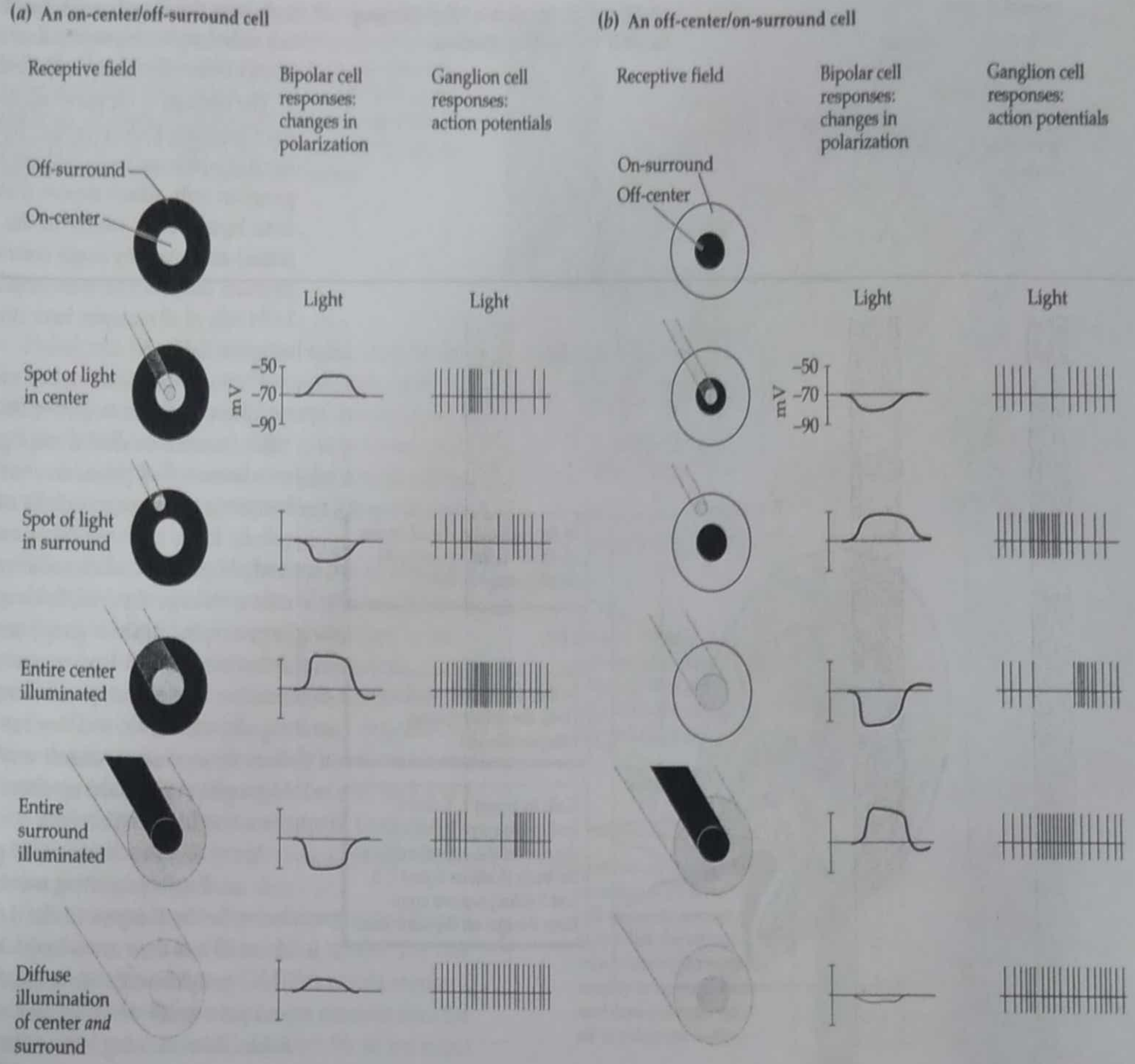
occipital cortex Also called *visual cortex*. The cortex of the occipital lobe of the brain.

striate cortex Primary visual cortex (V1).

extrastriate cortex Visual cortex outside of striate cortex.

on-center/off-surround Referring to a concentric receptive field in which the center excites the cell of interest while the surround inhibits it.

off-center/on-surround Referring to a concentric receptive field in which the center inhibits the cell of interest while the surround excites it.


(a) An on-center/off-surround cell
Receptive field
Bipolar cell responses: changes in polarization
Ganglion cell responses: action potentials
Off-surround
On-center
Light
Light
Spot of light in center
-50
-70
-90
mV
Spot of light in surround
Entire center illuminated
Entire surround illuminated
Diffuse illumination of center *and* surround
(b) An off-center/on-surround cell
Receptive field
Bipolar cell responses: changes in polarization
Ganglion cell responses: action potentials
On-surround
Off-center
Light
Light
-50
-70
-90
mV

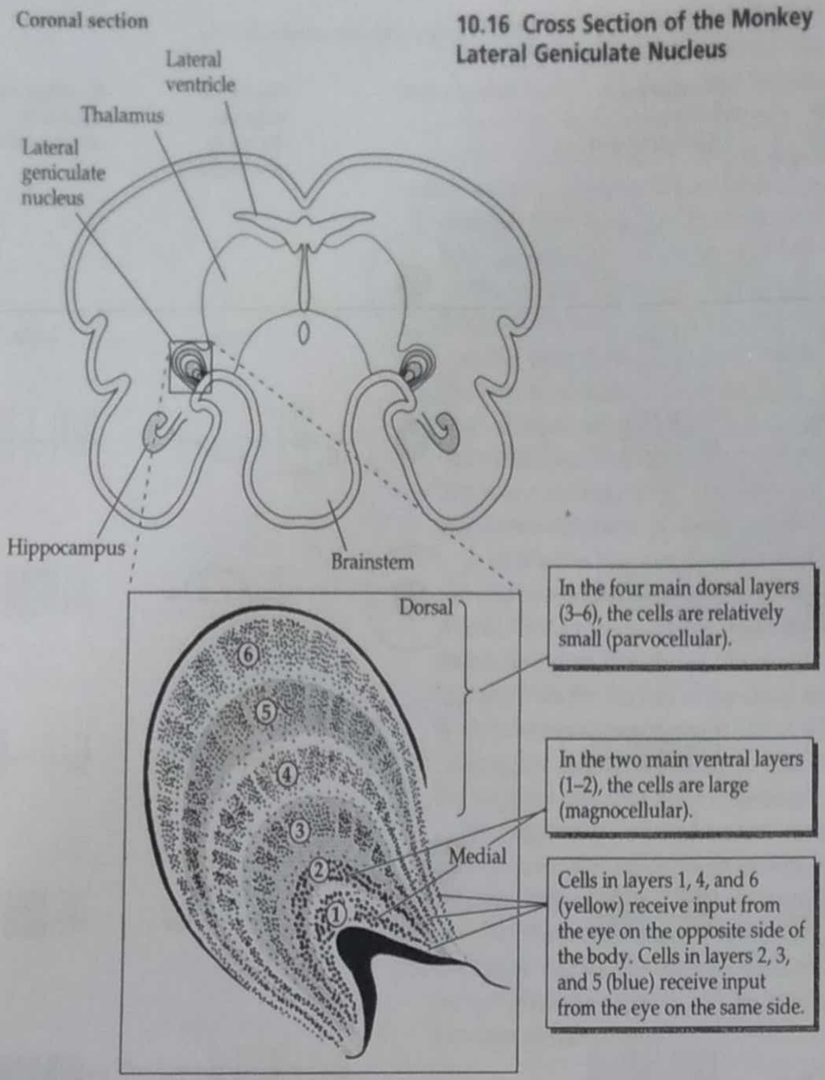
10.15 Receptive Fields of Retinal Cells In primates each retinal bipolar cell, as well as each retinal ganglion cell, has a concentric receptive field, with antagonistic center and surround. Here cells are shown responding to narrow or broad beams of light. Bipolar cells respond by changes in local membrane potentials; ganglion cells respond with action potentials. (*a*) An on-center/off-surround cell is excited by an increase of illumination in the center of its receptive field and inhibited by an increase of illumination in the surround. (*b*) Changes in illumination have the opposite effects on an off-center/on-surround cell.

Investigators who study primate visual systems take the organization of the LGN as their key. The primate LGN has six main layers and some smaller layers in between (**Figure 10.16**). The structure is called *geniculate* because the layers are bent like a knee, which in Latin is *genu*. The smaller layers are called *koniocellular layers* because they contain very small neurons (the Greek root *koni* means "dust").

The four dorsal, or outer, layers of the primate LGN are called **parvocellular** (from the Latin *parvus*, "small") because their cells are relatively small. The two ventral, or inner, layers are called **magnocellular** (from the Latin *magnus*, "large") because their cells are large. Most of the neurons in the magnocellular layers have relatively large receptive fields, the input of which can be traced back to large ganglion cells, which receive their input from retinal bipolar cells that contact many neighboring receptor cells. Most mag-

parvocellular Of or consisting of relatively small cells.

magnocellular Of or consisting of relatively large cells.



In the four main dorsal layers (3–6), the cells are relatively small (parvocellular).

In the two main ventral layers (1–2), the cells are large (magnocellular).

Cells in layers 1, 4, and 6 (yellow) receive input from the eye on the opposite side of the body. Cells in layers 2, 3, and 5 (blue) receive input from the eye on the same side.

10.16 Cross Section of the Monkey Lateral Geniculate Nucleus

nocellular neurons do not show differential wavelength responses; that is, they cannot be involved in color discrimination.

The neurons of the parvocellular layers have relatively small receptive fields, the input of which can be traced back to small ganglion cells, which receive their input from bipolar cells, which (in the central retina) are driven by single cones. These neurons discriminate wavelengths. The LGN cells of all six layers have concentric receptive fields.

There are two main types of retinal ganglion cells (Leventhal, 1979; Perry et al., 1984), sometimes called *M* and *P* ganglion cells because they project their axons, respectively, to the magnocellular or parvocellular layers of the LGN. As noted already, M ganglion cells are relatively large cells with large dendritic fields and thus large receptive fields. M ganglion cells can detect stimuli with low contrast and are sensitive to rapid temporal change; they respond transiently, and they have large-diameter axons that conduct very rapidly. M ganglion cells make up about 10% of primate retinal ganglion cells.

About 80% of primate retinal ganglion cells are P cells projecting most of their axons to the P layers of the LGN and about 10% of their axons to the M layers. The P ganglion cells are relatively small and have small dendritic and receptive fields. The remaining 10% of the primate ganglion cells are konio (K) cells, which project in three different bands from the retina to the LGN and visual cortex.

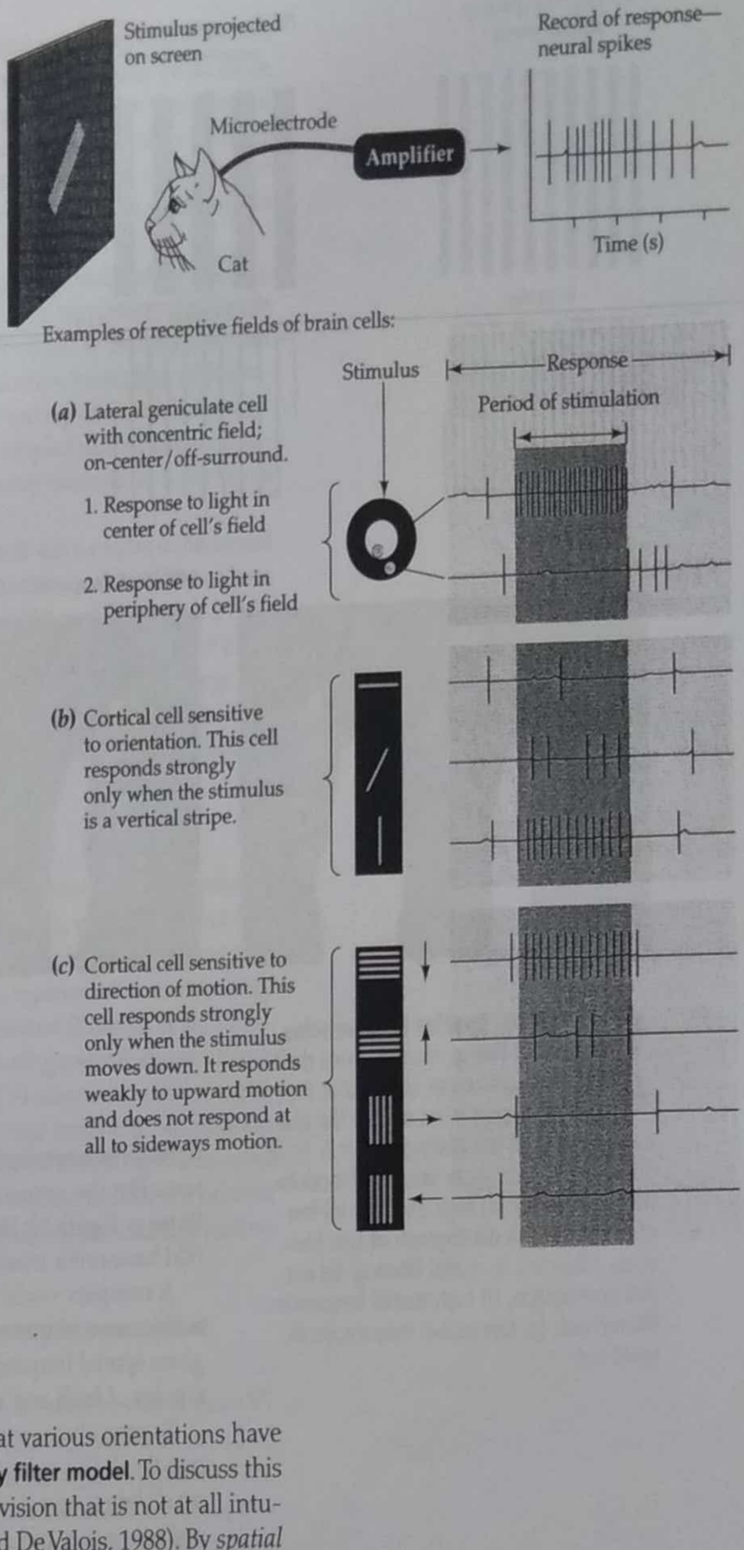
Neurons in the visual cortex have varied and complicated receptive fields

The next level of the visual system, the primary visual cortex, provided a puzzle. Neurons from the LGN send their axons to cells in the primary visual cortex (V1), but the spots of light that are effective stimuli for LGN cells (**Figure 10.17*a***) are not very effective for cortical cells. In 1959, David Hubel and Torsten Wiesel reported that visual cortical cells require more-specific, elongated stimuli than those that activate LGN cells. Most cells in area V1 respond best to lines or bars in a particular position and at a particular orientation in the visual field (**Figure 10.17*b***). Some cortical cells also require movement of the stimulus to make them respond actively. For some of these cells, any movement in their field is sufficient; others are more demanding, requiring motion in a specific direction (**Figure 10.17*c***). For this and related research, Hubel and Wiesel were awarded the Nobel Prize in Physiology or Medicine in 1981.

Hubel and Wiesel categorized cortical cells according to the types of stimuli required to produce maximum responses. So-called **simple cortical cells** responded best to an edge or a bar that had a particular width and a particular orientation and location in the visual field. These cells were therefore sometimes called *bar detectors* or *edge detectors*. Like the simple cells, **complex cortical cells** had elongated receptive fields, but they also showed some latitude for location; that is, they responded to a bar of a particular size and orientation anywhere within a larger area of the visual field.

simple cortical cell Also called *bar detector* or *edge detector*. A cell in the visual cortex that responds best to an edge or a bar that has a particular width, as well as a particular orientation and location in the visual field.

complex cortical cell A cell in the visual cortex that responds best to a bar of a particular size and orientation anywhere within a particular area of the visual field.


Stimulus projected on screen
Record of response—neural spikes
Microelectrode
Amplifier
Cat
Time (s)
Examples of receptive fields of brain cells:
Stimulus
Response
Period of stimulation
(a) Lateral geniculate cell with concentric field; on-center/off-surround.
1. Response to light in center of cell's field
2. Response to light in periphery of cell's field
(b) Cortical cell sensitive to orientation. This cell responds strongly only when the stimulus is a vertical stripe.
(c) Cortical cell sensitive to direction of motion. This cell responds strongly only when the stimulus moves down. It responds weakly to upward motion and does not respond at all to sideways motion.

10.17 Receptive Fields of Cells at Various Levels in the Cat Visual System Microelectrode recordings reveal that cells differ greatly in their receptive fields. (a) Visual cells in the lateral geniculate nucleus (LGN) have concentric receptive fields. (*b*) Visual cells in the cerebral cortex may show orientation specificity or respond only to motion, or (c) they may respond only to motion in a particular direction.

Hubel and Wiesel's theoretical model can be described as hierarchical; that is, more-complex events are built up from inputs of simpler ones. For example, a simple cortical cell can be thought of as receiving input from a row of LGN cells, and a complex cortical cell can be thought of as receiving input from a row of simple cortical cells.

Other theorists extrapolated from this model, suggesting that higher-order circuits of cells could detect any possible form. Thus it was suggested that, by integration of enough successive levels of analysis, a unit could be constructed that would enable a person to recognize his or her grandmother, and such hypothetical "grandmother cells" were frequently mentioned in the literature. According to this view, whenever such a cell was excited, up would pop a picture of one's grandmother. This hypothesis was given as a possible explanation for facial recognition.

Critics soon pointed out both theoretical and empirical problems with the hierarchical model. For one thing, a hierarchical system like this would require a vast number of cells—perhaps more neurons than the cortex possesses—in order to account for all the visual objects that one may encounter. At the same time that problems with this model were being identified, an alternative model was emerging, which we will describe next.

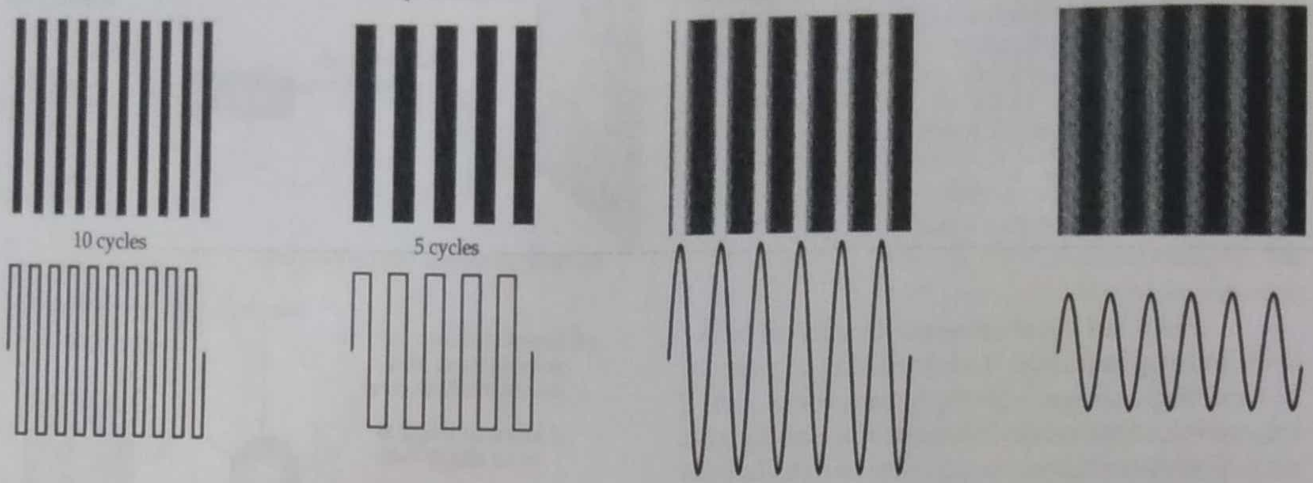
Most cells in the primary visual cortex are tuned to particular spatial frequencies

Concepts of pattern analysis in terms of lines and edges at various orientations have largely given way to what is known as the **spatial-frequency filter model**. To discuss this model, we must become familiar with a way of regarding vision that is not at all intuitive (F. W. Campbell and Robson, 1968; R. L. De Valois and De Valois, 1988). By *spatial frequency of a visual stimulus*, we mean the number of light–dark (or color) cycles that the stimulus shows per degree of visual space.

For example, Figure 10.18*a* and *b* differ in the spacing of the bars: **Figure 10.18*a*** has twice as many bars in the same horizontal space and is therefore said to have double the spatial frequency of **Figure 10.18*b***. The spatial-frequency technique applies Fourier analysis (see Box 9.1) or linear systems theory, rather than analyzing visual patterns into bars and angles.

In Box 9.1 we saw that we can produce any complex, repeating auditory stimulus by adding together simple sine waves. Conversely, using Fourier analysis, we can determine which combination of sine waves would be needed to make any particular complex waveform. The same principle of Fourier analysis can be applied to visual patterns.

spatial-frequency filter model A model of pattern analysis that emphasizes Fourier analysis of visual stimuli.

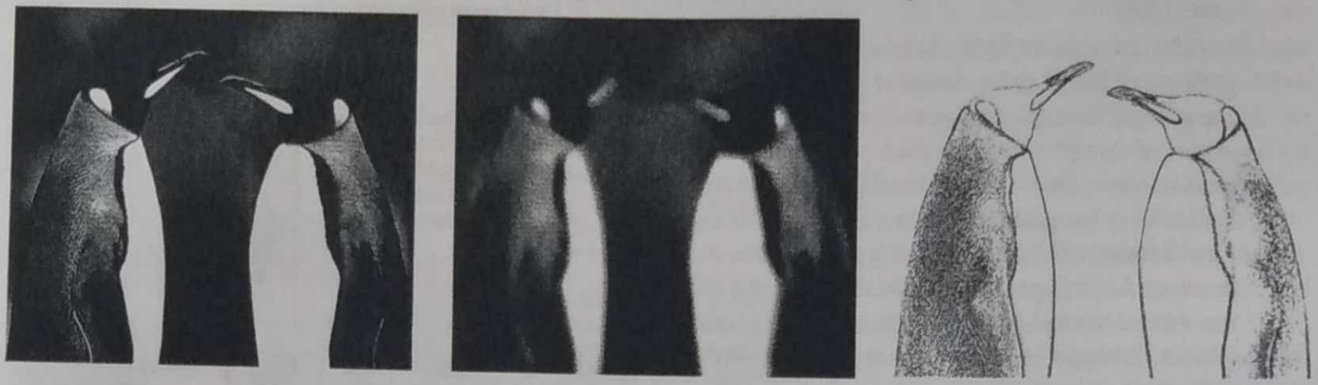


(*a*) High-frequency square wave

(*b*) Low-frequency square wave

(*c*) High-contrast sinusoidal spatial grid

(*d*) Low-contrast sinusoidal spatial grid



(*e*) Normal

(*f*) High frequencies filtered out

(*g*) Low frequencies filtered out

10.18 Spatial Frequencies (*a, b*) The spacing between dark and light stripes shows that the grating in part *a* has double the spatial frequency of the grating in part *b*. (*c, d*) These visual grids show sinusoidal modulation of intensity: (*c*) high contrast; (*d*) low contrast. (*e–g*) A photograph of two penquins subjected to spatial filtering: (*e*) normal photograph; (*f*) high spatial frequencies filtered out; (*g*) low spatial frequencies filtered out.

If the dimension from dark to light varies according to a sine wave function, visual patterns like the ones in **Figure 10.18*c* and *d*** result. A series of dark and light stripes, like those in Figure 10.18*a* and *b*, can be analyzed into the sum of a visual sine wave and its odd harmonics (multiples of the basic frequency).

A complex visual pattern or scene can also be analyzed by the Fourier technique; in this case, frequency components at different angles of orientation are also used. A given spatial frequency can exist at any level of contrast; Figure 10.18*c* and *d* show examples of high and low contrast, respectively.

To reproduce or perceive a complex pattern or scene accurately, the system has to handle all the spatial frequencies present. If the high frequencies are filtered out, the small details and sharp contrasts are lost; if the low frequencies are filtered out, the large uniform areas and gradual transitions are lost. **Figure 10.18e–g** show how the filtering of spatial frequencies affects a photograph. The photograph is still recognizable after either the high visual frequencies (Figure 10.18*f*) or low frequencies (Figure 10.18*g*) are filtered out. (Similarly, speech is still recognizable, although it sounds distorted, after either the high audio frequencies or the low frequencies are filtered out.)

F. W. Campbell and J. G. Robson (1968) suggested that the visual system includes many channels tuned to different spatial frequencies, just as the auditory system has channels for different acoustic frequencies. The term *channel* is used here to mean a mechanism that accepts or deals with only a particular band or class of information. This concept is analogous to the transmission of information by a particular radio or television station, which uses an assigned channel, or band of wavelengths; to receive this information, you must tune your receiving device to the particular channel.

The suggestion that the nervous system has different spatial-frequency channels was soon supported by experiments on selective adaptation to spatial patterns (Blakemore and Campbell, 1969; Pantle and Sekuler, 1968). In these experiments a person spent a minute or more inspecting a visual grating with a given spacing (or spatial frequency), such as those in Figure 10.18*a* and *b*. Looking at the grating made the cells that are tuned to that frequency adapt (become less sensitive). Then the person's sensitivity to gratings of different spacings was determined.

The results showed that sensitivity to the subsequent gratings was reduced briefly at the particular frequency to which the person had adapted. The suggestion of multiple spatial-frequency channels had revolutionary impact because it led to entirely different conceptions of the way in which the visual system might function in dealing with spatial stimuli. The idea suggests that, rather than specifically detecting such seminaturalistic features as bars and edges, the system is breaking down complex stimuli into their individual spatial-frequency components in a kind of crude Fourier analysis (R. L. De Valois and De Valois, 1988, p. 320).

The responses of cortical cells to spatial-frequency stimuli were found to be tuned more accurately to the dimensions of spatial-frequency grids than to the widths of bars (R. L. De Valois et al., 1977; Hochstein and Shapley, 1976; Maffei and Fiorentini, 1973). The receptive field of a cortical cell typically shows an excitatory axis and bands of inhibition on each side; the spacing of these components shows the frequency tuning. The spatial-frequency approach has proven useful in the analysis of many aspects of human pattern vision (K. K. De Valois et al., 1979), and it provides the basis of high-definition television (HDTV).

Area V1 is involved in the formation of mental images

Neurons of V1 (the primary visual cortex) appear to be involved not only in perceiving objects and events, but also in forming mental images. For example, imagined objects activate regions that correspond to the retinotopic mapping of V1; when people imagined small letters, PET recording showed activation of the foveal representation; when they imagined large letters, the parafoveal representation was activated (Kosslyn et al., 1993).

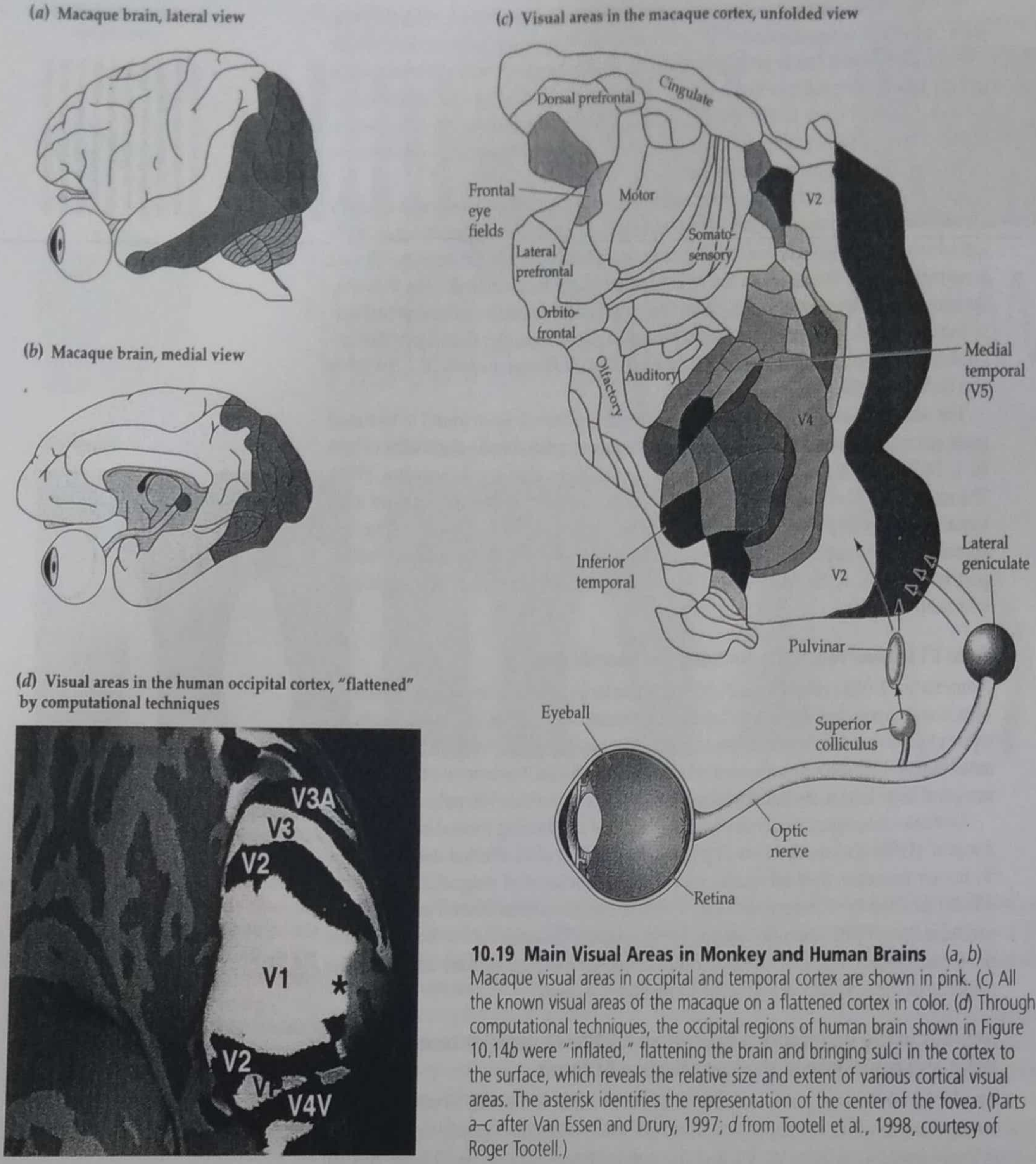
To obtain convergent evidence about the role of V1 in forming mental images, Kosslyn et al. (1999) also studied how impairing the function of V1 affected mental images. To impair function, they administered repetitive transcranial magnetic stimulation (rTMS) directed to V1. Before each set of trials in which subjects formed and inspected mental images, rTMS was administered for 10 minutes. This stimulation did not prevent the formation of images, but it significantly impaired the process, thus adding further evidence of the necessity of V1 for the formation of images.

Neurons in the visual cortex beyond area V1 have complex receptive fields and contribute to the identification of forms

Area V1 is only a small part of the portion of cortex that is devoted to vision. Area V1 sends axons to other visual cortical areas, including areas that appear to be involved in the perception of form: V2, V4, and the inferior temporal area (see Figure 10.19*c*). Some of these extrastriate areas also receive direct input from the LGN. The receptive fields of the cells in many of these extrastriate visual areas are even more complex than those in cells of area V1. As **Figure 10.19*a*–*c*** reflect, on the basis of anatomical, physiological, and behavioral investigations with macaque monkeys, we know that at least 32 distinct cortical areas are directly involved in visual function (Van Essen and Drury, 1997).

The visual areas of the human brain (**Figure 10.19*d***) have been less thoroughly mapped than those of the monkey brain, and mainly by neuroimaging (the spatial resolution of which is not as fine as that of the electrophysiological recording used in the monkey brain), but the general layout appears to be similar in the two species. However, the similarities are greatest for V1 and adjacent regions and fall off for other areas (Tootell et al., 2003).

In addition, the proportions of cortical areas between the two species show important differences. In macaque monkeys, the occipital lobe occupies about 32% of the iso-


(*a*) Macaque brain, lateral view

(*b*) Macaque brain, medial view

(*c*) Visual areas in the macaque cortex, unfolded view

(*d*) Visual areas in the human occipital cortex, "flattened" by computational techniques

Cingulate
Dorsal prefrontal
Frontal eye fields
Motor
V2
Somato-sensory
Lateral prefrontal
Orbito-frontal
Olfactory
Auditory
V3
Medial temporal (V5)
V4
Inferior temporal
V2
Lateral geniculate
Pulvinar
Eyeball
Superior colliculus
Optic nerve
Retina
V3A
V3
V2
V1
*
V2
V1
V4V

10.19 Main Visual Areas in Monkey and Human Brains (*a, b*) Macaque visual areas in occipital and temporal cortex are shown in pink. (*c*) All the known visual areas of the macaque on a flattened cortex in color. (*d*) Through computational techniques, the occipital regions of human brain shown in Figure 10.14*b* were "inflated," flattening the brain and bringing sulci in the cortex to the surface, which reveals the relative size and extent of various cortical visual areas. The asterisk identifies the representation of the center of the fovea. (Parts *a–c* after Van Essen and Drury, 1997; *d* from Tootell et al., 1998, courtesy of Roger Tootell.)

cortex (neocortex), and the frontal lobe about 26%; in humans, the occipital lobe occupies about 19%, and the frontal lobe about 36%. Whereas the 32 areas that are largely or entirely visual in function occupy about 55% of the surface of the macaque cortex, the visual areas account for only about 30% of human cortex (Tootell et al., 2003). We will discuss only a few of the main visual cortical areas and their functions.

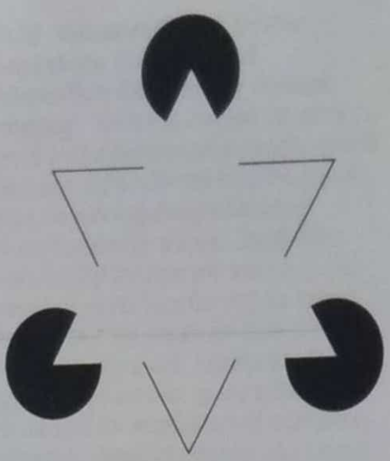
Area V2 is adjacent to V1, and many of its cells show properties similar to those of V1 cells. Many V2 cells can respond to illusory contours, which may help explain how we perceive contours such as the boundaries of the upright triangle in **Figure 10.20** (Peterhans and von der Heydt, 1989). Clearly such cells respond to complex relations among the parts of their receptive fields. Some V1 cells can also respond to illusory contours (Grosof et al., 1993), but this feature is more common in area V2.

Area V4 receives axons from V2 and has cells that give their strongest responses to the sinusoidal frequency gratings that we discussed earlier (see Figure 10.18*c* and *d*). However, many V4 cells given even stronger responses to concentric and radial stimuli, such as those in **Figure 10.21a** (Gallant et al., 1993). Investigators have suggested that these V4 cells show an intermediate stage between the spatial-frequency processing in V1 and V2 cells and the recognition of pattern and form in cells of the inferior temporal area. Area V4 also has many cells that respond most strongly to wavelength differences, as we will see later when we discuss color vision. Area V5, also called the *medial temporal* (*MT*) *area*, appears to be specialized for the perception of motion, as we will also discuss later in this chapter.

The inferior temporal (IT) visual cortex has many cells that respond best to particular complex forms, including forms that the subject has learned to recognize. Because many cells in IT cortex have highly specific receptive fields, it is hard to find the exact stimuli that can activate a particular cell. Experimenters start by presenting many three-dimensional animal and plant objects (Desimone et al., 1984; K. Tanaka, 1993). When a stimulus elicits a strong response, the experimenters then simplify the image by sequentially removing parts of the features to determine the necessary and sufficient features for maximal activation of the cell.

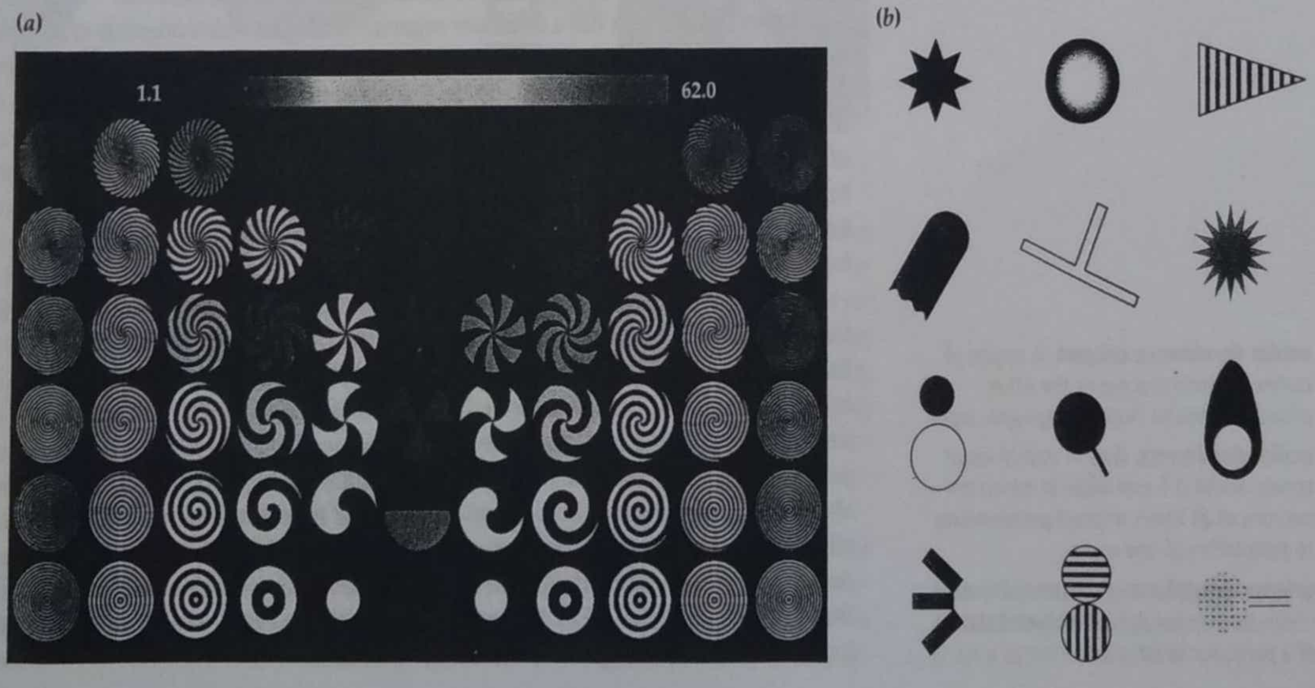
Most cells in IT cortex do not require a natural object such as a face to activate them; instead they require moderately complex shapes, sometimes combined with color or texture, such as those in **Figure 10.21*b***. The complex receptive fields in IT cortex probably develop through experience and learning. After a monkey was trained for a year to discriminate a set of 28 moderately complex shapes, 39% of the cells in its anterior IT cortex responded significantly to some of these shapes. In control monkeys, on the other hand, only 9% of the cells responded strongly to these forms (Kobatake and Tanaka, 1994).

The prefrontal cortex also contains a restricted region of neurons that are activated by faces but not by other visual stimuli, as found both by noninvasive recording of human subjects (Ungerleider et al., 1998) and by electrical recording of neurons in the monkey brain (Scalaidhe et al., 1997). These neurons receive connections from the superior temporal sulcus and adjacent cortex on the inferior temporal gyrus. These findings indicate that a visual pathway that processes visual recognition extends from the primary visual cortex through temporal cortical regions to the prefrontal cortex. Later we'll see that this is the ventral pathway that was damaged in D.F.



10.20 A Geometric Figure with "Illusory" or "Subjective" Contours Cells have been found in visual cortical areas that respond to illusory contours such as those of the upright triangle shown here. These contours thus have neurophysiological meaning.

10.21 Complex Stimuli Evoke Strong Responses in Visual Cortex (*a*) These concentric and radial stimuli evoke maximal responses from some cells in visual cortical area V4. The stimuli that evoked the highest response rates (see scale bar) are shown in red and orange. (*b*) These 12 examples illustrate the critical features of stimuli that evoke maximal responses from cells in the anterior inferior temporal area. (Part *a* from Gallant et al., 1993, courtesy of Jack Gallant; *b* from K. Tanaka, 1993, courtesy of Keiji Tanaka.)



Area V1 Is Organized in Columns and Slabs

The primary visual cortex has separate representations for at least four dimensions of the visual stimulus: (1) location in the visual field, with larger, finer mapping of the central region of the visual field than of the periphery; (2) ocular dominance; (3) orientation; and (4) color.

Ocular dominance columns were first discovered by electrophysiological recording. Although the receptive field of an individual neuron is the same for vision through either eye, some cells are equally activated by the two eyes but other cells respond preferentially (i.e., more strongly) to stimulation of one eye. However, all the cells in a vertical column of cells have the same ocular dominance. The vertical columns are arranged into **ocular dominance slabs** about 0.5 mm wide, all cells of which respond preferentially to stimulation of one eye. A given point in the visual field elicits responses in cells in adjacent left-eye-preferring and right-eye-preferring ocular dominance slabs.

Ocular dominance is especially clear in the broad layer IV, where each cell is monocular, responding to only one eye. Above and below the (monocular) ocular dominance stripes in layer IV, most of the cells respond to stimulation of both eyes but still prefer one eye over the other.

Optical imaging of cortical activity (T. Bonhoeffer and Grinvald, 1991; Ts'o et al., 1990) allows us to see the ocular dominance stripes in the primary visual cortex of an awake monkey (**Figure 10.22*a* and *b***). The imaging is based on small changes in the light reflected from the cortex during activity. These changes are of two types: (1) changes in blood volume, probably in the capillaries of the activated area; and (2) changes in cortical tissue, such as the movement of ions and water or the expansion and contraction of extracellular spaces. Experimenters can combine optical imaging with electrophysiological recording to place microelectrodes in particular parts of ocular dominance slabs. Figure 10.22*b* shows the ocular dominance columns that were activated when one eye was stimulated. This recording technique may prove useful as a mapping tool in human neurosurgery.

Ocular dominance columns develop during the first 4 months of life in the cat and during the first 6 months in the macaque monkey. As we saw in Chapter 7, both eyes must be exposed to the visual environment if each eye is to obtain its own cortical representation (see Figure 7.20). Up to the age of 3 or 4 months, human infants are unimpressed by stereograms (pairs of pictures showing somewhat different left-eye and right-eye views that most adult observers perceive as a three-dimensional view). Beginning at the age of 3 or 4 months, however, most infants are captivated by stereograms (Held, 1993). Presumably, before that age the cortex is unable to separate the information from the two eyes because the information reaches the same cortical neurons.

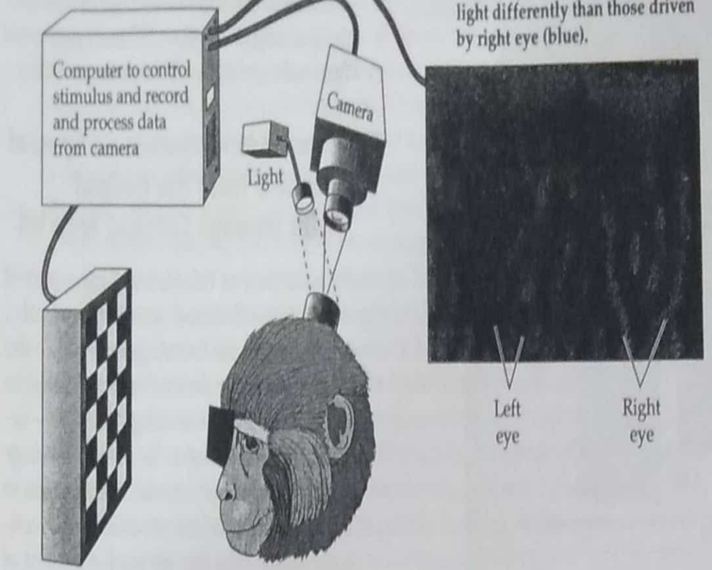
Primary visual cortex has a columnar organization for stimulus orientation as well: a microelectrode that follows a path perpendicular to the surface records cells that all prefer the same stimulus orientation within the visual field (**Figure 10.22*c* and *d***). As the recording electrode is moved from one **orientation column** to the next, the preferred axis of orientation shifts by a few degrees. That is, in one column all the cells may be "tuned" to upright stimuli (at an orientation of 0°); in an adjacent column, all cells may respond best to another orientation, perhaps at 10° from the vertical; in the next column, perhaps at 25°; and so forth.

In Figure 10.22*d* we see how these columns are organized parallel to the surface of the cortex. In this figure, optical recordings show the regions of primary visual cortex that respond best to stimuli of four different orientations. The columns are organized into slabs that run perpendicular to the borders of ocular dominance columns. These slabs, however, stretch only from the center of one ocular stripe to the center of the adjacent stripe. Along the center of the ocular dominance stripes, preferred orientation shifts by 90°, creating regularly spaced "pinwheels" in which responses to the different stimulus orientations pivot around a center. A striking technical advance in the functional-MRI technique made it possible to visualize individual orientation columns in the visual cortex of cats (D.-S. Kim et al., 2000), showing excellent agreement with data from electrical recording and optical imaging studies.

ocular dominance column A region of cortex in which one eye or the other provides a greater degree of synaptic input.

ocular dominance slab A slab of visual cortex, about 0.5 mm wide, in which the neurons of all layers respond preferentially to stimulation of one eye.

orientation column A column of visual cortex that responds to rod-shaped stimuli of a particular orientation.



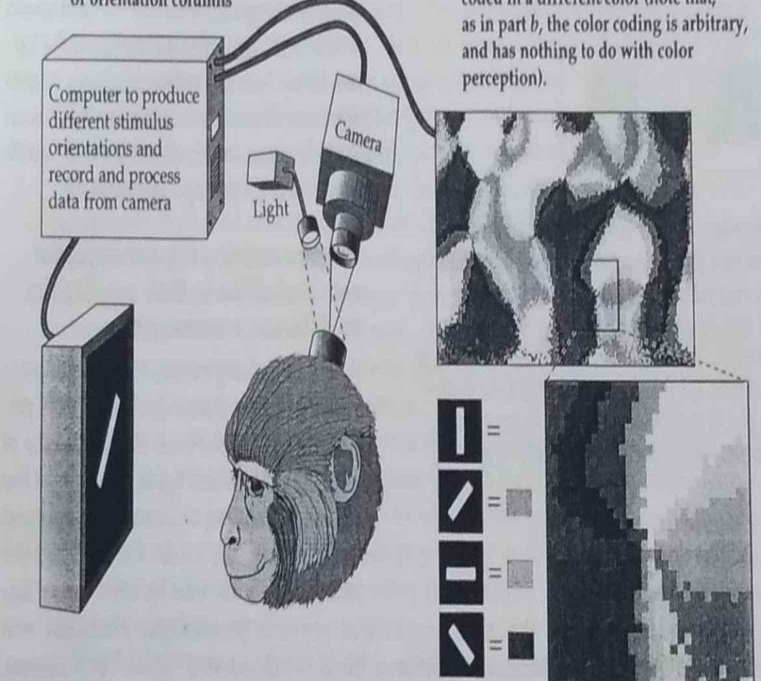
(*a*) Method for visualization of ocular dominance columns

(*b*) Cortical regions driven by left eye (red) are more active, require a greater blood supply, and therefore reflect light differently than those driven by right eye (blue).

Computer to control stimulus and record and process data from camera
Camera
Light
Left eye
Right eye

(*c*) Method for visualization of orientation columns

(*d*) Cortical regions driven by stimuli in four different orientations are each coded in a different color (note that, as in part *b*, the color coding is arbitrary, and has nothing to do with color perception).



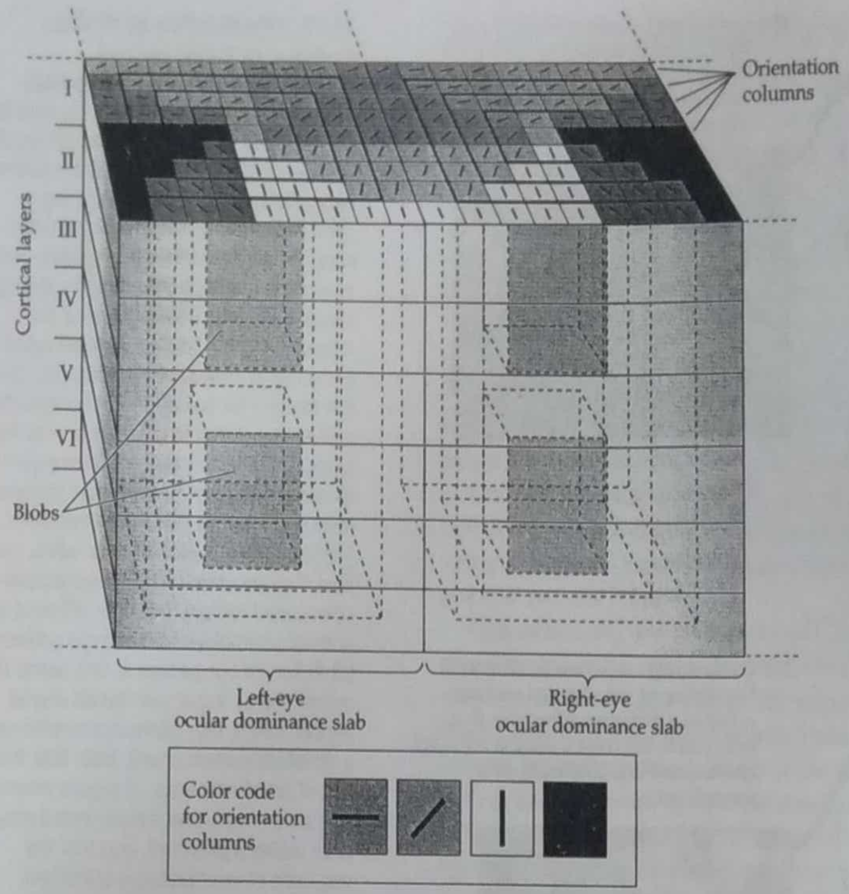
Computer to produce different stimulus orientations and record and process data from camera
Camera
Light
=
=
=
=

10.22 Visualization of Ocular Dominance Columns and Orientation Columns by Optical Imaging (a) In this method for visualization of ocular dominance, a camera records changes in light reflected from the cortex when the monkey views a twinkling checkerboard with one eye. Small differences in reflected light are amplified, and intensity is coded by color (red for strong intensity, blue for weak). (*b*) After the recording is processed, regions activated by the active eye are seen as red stripes. (c) In this method for visualization of orientation preference, stimuli at different orientations (vertical, horizontal, diagonal) are presented to reveal groups of neurons that respond most strongly to a particular orientation. The stimuli are usually black or white, but here they are color-coded to correspond to color-coded responses to four different orientations combined into a single pattern. (*d*) Although the pattern at first seems disorderly, closer inspection reveals several regions where four orientations converge in a pinwheel pattern (inset). Note that the foci of pinwheels occur at regular intervals, that each orientation is represented only once within a pinwheel, and that the sequence of orientations is consistent across pinwheels. (After T. Bonhoeffer and Grinvald, 1991; *b* and *d* courtesy of A. Grinvald.)

Also within the ocular dominance slabs of primate visual areas are vertical **blobs** (sometimes called *pegs*) that can be seen when the tissue is stained to reveal the enzyme cytochrome oxidase. Early experiments suggested that the blobs were related to color vision (Hendrickson, 1985; Livingstone and Hubel, 1984), but later work has cast doubt on this hypothesis. Quantitative studies show that neurons in the blobs cannot be readily distinguished from neurons outside the blobs on the basis of either chromatic tuning (Lennie et al., 1990) or orientation tuning (Leventhal et al., 1995). In addition, even nocturnal primates (which have few cones in their retinas) and cats (which have little color vision) have blobs; and cone-rich rodents, such as ground squirrels, do not have blobs.

Blobs extend above and below layer IV but are not seen in layer IV itself. **Figure 10.23** diagrams the organization of the primate primary visual cortex, including the large ocular dominance slabs, the orientation columns, and the blobs. Along the centers of the ocular dominance slabs, the orientation columns are arranged radially, like the “pin-

blob Also called *peg*. A region of visual cortex distinguished by stains for the enzyme cytochrome oxidase.


Orientation columns
Cortical layers
I
II
III
IV
V
VI
Blobs
Left-eye ocular dominance slab
Right-eye ocular dominance slab
Color code for orientation columns

10.23 Organization of the Primate Primary Visual Cortex These two partial ocular dominance slabs represent the left and right eyes, respectively. Blobs extend vertically through layers I through III and V through VI, located in the centers of ocular dominance slabs. Small columns represent the preferred orientations of groups of cells; these orientation columns radiate from the centers of the blobs. The orientation is color-coded here as in Figure 10.22*d*. For simplification, this diagram does not represent spatial frequency (higher spatial frequencies occur at the edges of the blocks and lower frequencies in the centers), nor does it represent the spectrally opponent cells (which we'll discuss shortly) that occur irregularly in the columns.

wheels" in Figure 10.21*d*, with blobs at the centers of the pinwheels; but elsewhere the orientation columns are laid out in a rectangular arrangement, like city blocks that cross the borders of the ocular dominance slabs.

Color Vision Depends on Special Channels from the Retinal Cones through Cortical Area V4

For most people, color is a striking aspect of vision. We will discuss four stages of color perception. In the first stage the cones—the retinal receptor cells that are specialized to respond to certain wavelengths of light—receive visual information. In the second stage this information is processed by neurons in the local circuits of the retina, leading to retinal ganglion cells that are excited by light of some wavelengths and inhibited by light of other wavelengths. The ganglion cells send the wavelength information via their axons to the LGN, mainly in the parvocellular layers. From there this information goes to area V1, from which it is relayed to other visual cortical areas, where the third and fourth stages of color perception take place.

Color perception requires receptor cells that differ in their sensitivities to different wavelengths

Artists have long known that all the hues can be obtained from a small number of primary colors. On the basis of observations of mixing pigments and lights, scientists at the start of the nineteenth century hypothesized that three separate kinds of receptors in the retina provide the basis for color vision. Endorsed in 1852 by the great physiologist-physicist-psychologist Hermann von Helmholtz, this **trichromatic hypothesis** (from the Greek *tri-*, "three," and *chroma*, "color") became the dominant position.

Helmholtz predicted that blue-sensitive, green-sensitive, and red-sensitive receptors would be found, that each would be sharply tuned to its part of the spectrum, and that each type would have a separate path to the brain. The color of an object would be recognized, then, on the basis of which color receptor was activated. This system would be like the mechanisms for discriminating touch and temperature on the basis of which skin receptors and labeled neural lines are activated (see Chapter 8).

Later in the nineteenth century, physiologist Ewald Hering proposed a different explanation. He argued, on the basis of visual experience, that there are four unique hues and three opposed pairs of colors—blue versus yellow, green versus red, and black versus white—and that three physiological processes with opposed positive and negative values must therefore be the basis of color vision. As we will see, both this **opponent-process hypothesis** and the trichromatic hypothesis are encompassed in current color vision theory, but neither of the old hypotheses is sufficient by itself.

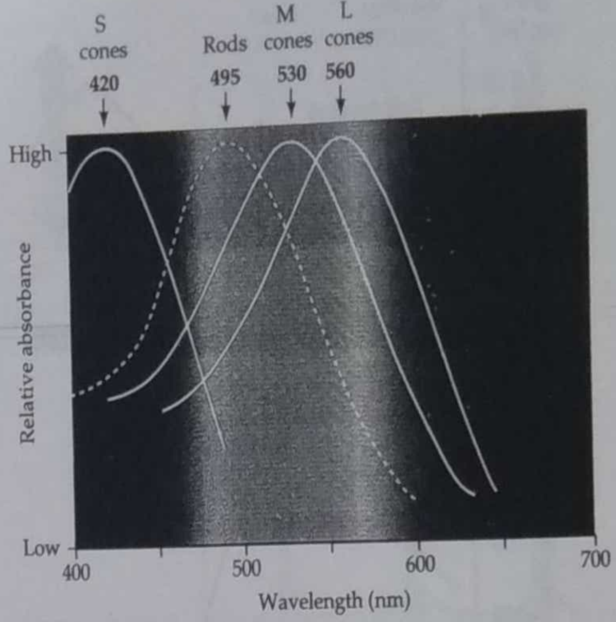
Measurements of photopigments in cones have borne out the trichromatic hypothesis in part. Each cone of the human retina has one of three classes of pigments. These

trichromatic hypothesis A hypothesis of color perception stating that there are three different types of cones, each excited by a different region of the spectrum and each having a separate pathway to the brain.

opponent-process hypothesis The theory that color vision depends on systems that produce opposite responses to light of different wavelengths.

pigments do not, however, have the narrow spectral distributions that Helmholtz predicted. The color system that Helmholtz postulated would have given rather poor color vision and poor visual acuity. Color vision would be poor because only a few different hues could be discriminated; within the long-wavelength region of the spectrum there would be only red, and not all the range of hues that we see. Acuity would be poor because the grain of the retinal mosaic would be coarse; a red stimulus would be able to affect only one-third of the receptors. (In reality, though, acuity is as good in red light as it is in white light.)

The human visual system does not have receptors that are sensitive to only a narrow part of the visible spectrum. Two of the three retinal cone pigments show some response to light of almost *any* wavelength. The pigments have different *peaks* of sensitivity, but the peaks are not as far apart as Helmholtz predicted. As **Figure 10.24** shows, the peaks occur at about 420 nm (in the part of the spectrum where we usually see violet under photopic conditions), about 530 nm (where most of us see green), and about 560 nm (where most of us see yellow-green). Despite Helmholtz's prediction, none of the curves peak in the long-wavelength part of the spectrum, where most of us see red (about 630 nm).



10.24 Spectral Sensitivities of Human Photopigments Each pigment has a peak sensitivity but responds to a wide range of wavelengths. S, short-wavelength; M, medium-wavelength; L, long-wavelength.

Under ordinary conditions, almost any visual object stimulates at least two kinds of cones, thus ensuring high visual acuity and good perception of form. The spectral sensitivities of the three cone types differ from each other, and the nervous system detects and processes these differences to extract the color information. Thus, certain ganglion cells and certain cells at higher stations in the visual system are color-specific, even though the receptor cells are not. Similarly, visual receptors are not form-specific, but form is detected later in the visual centers by comparison of the outputs of different receptors.

Because the cones are not color detectors, the most appropriate brief names for them can be taken from their peak areas of wavelength sensitivity: *short* (S) for the receptor with peak sensitivity at about 420 nm, *medium* (M) for 530 nm, and *long* (L) for 560 nm (see Figure 10.24). There are typically twice as many L as M receptors, but far fewer S receptors (Brainard et al., 2000; Carroll et al., 2000; Hagstrom et al., 1998); this difference explains why acuity is much lower with short-wavelength illumination (blue light) than in the other parts of the visible spectrum.

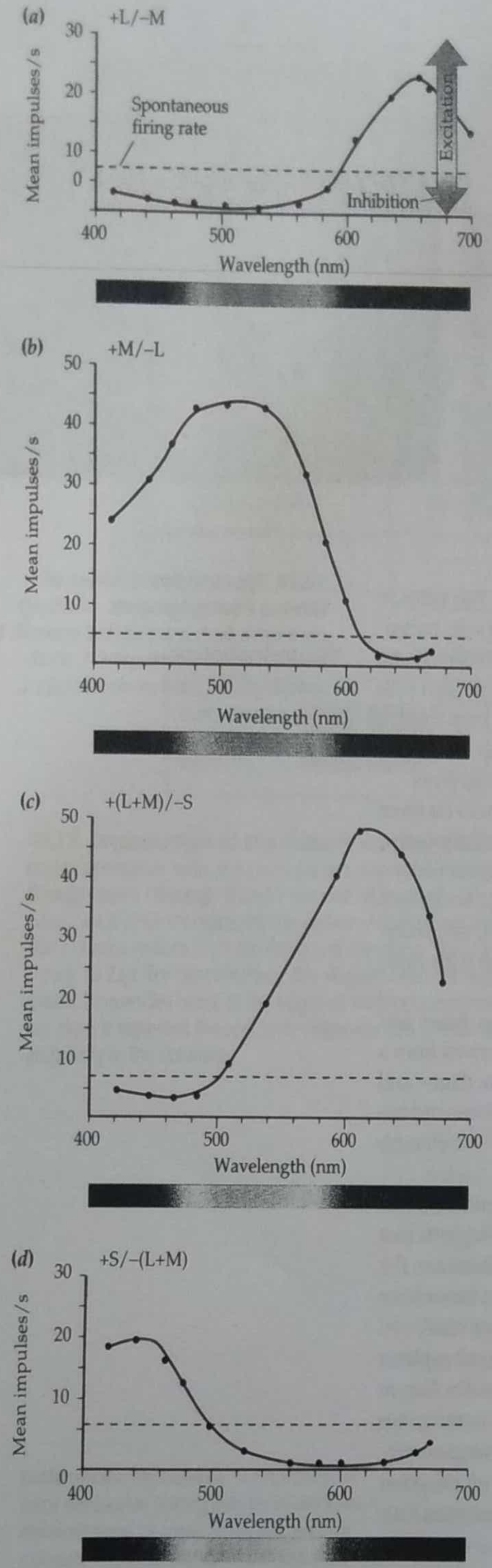
The genes for wavelength-sensitive pigments in the retina have been analyzed, and the similarities in structure of the three genes suggest that they are all derived from a common ancestral gene (Nathans, 1987). In addition, the genes for the medium- and long-wavelength pigments occupy adjacent positions on the X chromosome and are much more similar to each other than either is to the gene for the short-wavelength pigment on chromosome 6.

The fact that humans and Old World monkeys have both M and L pigments, whereas most New World monkeys have only a single longer-wavelength pigment, suggests that the M and L pigments differentiated recently in evolutionary terms. Furthermore, the genes for the M and L pigments are variable among individuals, and particular variants in these pigment genes correspond to variants in color vision: so-called color blindness.

The fact that the genes for the M and L pigments are on the X chromosome explains why defects of red/green color vision are much more frequent in human males than in human females. Because males have only one X chromosome, a mutation in the genes for the M or L pigments can impair color vision. But if a female has a defective photopigment gene in one of her two X chromosomes, a normal copy of the gene on the other X chromosome can compensate. Only rarely do both of a female's X chromosomes have defective genes for color receptors.

Some retinal ganglion cells and parvocellular LGN cells show spectral opponency

Recordings made from retinal ganglion cells in Old World monkeys, which can discriminate colors as humans do, reveal the second stage of processing of color vision. Most



10.25 Responses of the Four Main Types of Spectrally Opponent Cells in Monkey LGN The four main types of spectrally opponent cells are (a) +L/–M, (b) +M/–L, (c) +(L+M)/–S, and (d) +S/–(L+M). Each type is excited by one band of wavelengths and inhibited by another.

ganglion cells and cells in the parvocellular layers of the LGN fire in response to some wavelengths and are inhibited by other wavelengths.

Figure 10.25a shows the response of a parvocellular LGN cell as a large spot of light centered on its receptive field is changed from one wavelength to another. Firing is stimulated by wavelengths above 600 nm, where the L cones are most sensitive, then inhibited at shorter wavelengths, where the L cones are less sensitive than the M cones. A cell exhibiting this response pattern is therefore called a *plus L/minus M cell* (*+L/–M*). This is an example of a **spectrally opponent cell** because two regions of the spectrum have opposite effects on the cell's rate of firing. Figure 10.25 shows examples of responses of the four main kinds of spectrally opponent cells.

Each spectrally opponent ganglion cell receives input from two or three different kinds of cones through bipolar cells. The connections from at least one type of cone are excitatory, and those from at least one other type are inhibitory. The spectrally opponent ganglion cells thus record the *difference* in stimulation of different populations of cones. For example, a +M/–L cell responds to the difference in the excitation of M and L cones.

The peaks of the sensitivity curves of the M and L cones are not very different (see Figure 10.24). However, whereas the M-minus-L *difference* curve (**Figure 10.25*b***) shows a clear peak at about 500 nm (in the green part of the spectrum), the L-minus-M difference function (see Figure 10.25*a*) shows a peak at about 650 nm (in the red part of the spectrum). Thus, +M/–L and +L/–M cells yield distinctly different neural response curves. LGN cells excited by the L and M cells, but inhibited by S cells—that is, +(L+M)/–S cells—peak in the red range (**Figure 10.25*c***), while cells excited by S but inhibited by L and M—that is, +S/–(L+M) cells—peak in the blue-violet range (**Figure 10.25*d***).

Spectrally opponent neurons are the second stage in the system for color perception, but they still cannot be called *color cells*, for the following reasons: (1) they send their outputs into many higher circuits—for detection of form, depth, and movement, as well as hue; and (2) their peak wavelength sensitivities do not correspond precisely to the wavelengths that we see as the principal hues.

In addition to the four kinds of spectrally opponent ganglion cells, **Figure 10.26** diagrams the presumed inputs of ganglion cells that detect brightness and darkness. The brightness detectors receive stimulation from both M and L cones (+M/+L); the darkness detectors are inhibited by both M and L cones (–M/–L).

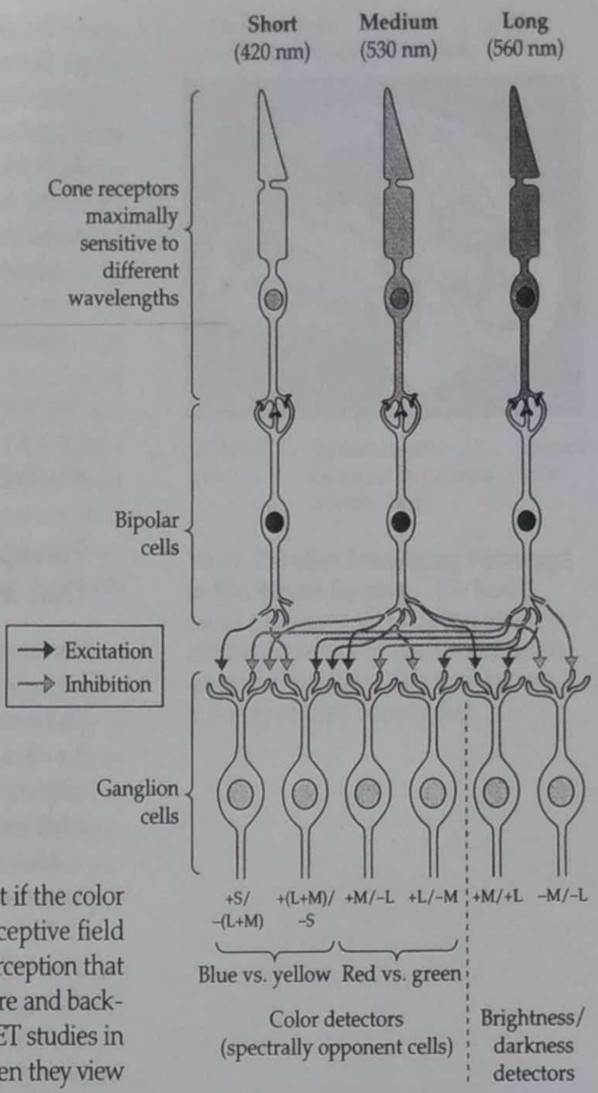
In the monkey LGN, 70% to 80% of the cells are spectrally opponent; in the cat, very few spectrally opponent cells are found—only about 1%. This difference explains the ease with which monkeys discriminate wavelengths and the difficulty in training cats to discriminate even large differences in wavelength.

Some visual cortical cells and regions appear to be specialized for color perception

In the cortex, spectral information appears to be used for various kinds of information processing. Forms are segregated from their background by

spectrally opponent cell A visual receptor cell that has opposite firing responses to different regions of the spectrum.

10.26 A Model of the Connections of Wavelength Discrimination Systems in the Primate Retina The connections from the cones yield four kinds of spectrally opponent ganglion cells, as well as ganglion cells that detect brightness or darkness. (After R. L. De Valois and De Valois, 1980.)



differences in color or intensity (or both). The most important role that color plays in our perception is to denote which parts of a complex image belong to one object and which belong to another. Some animals use displays of brightly colored body parts to call attention to themselves, but color can also be used as camouflage.

Some spectrally opponent cortical cells contribute to the perception of color, providing the third stage of the color vision system. Russell De Valois (1926–2003) and Karen De Valois have suggested ways in which adding and subtracting the outputs of spectrally opponent ganglion cells could yield cortical cells that are perceptually opponent: red versus green, blue versus yellow, and black versus white (R. L. De Valois and K. K. De Valois, 1993). The spectral responses of these cells correspond to the wavelengths of the principal hues specified by human observers, and their characteristics also help explain other color phenomena.

Visual cortical region V4 is particularly rich in color-sensitive cells. Electrophysiological recording in monkeys shows that only some V4 cells (probably a minority) are selective for color (Schein et al., 1982). Evidence that area V4 is normally involved in the perception of color comes from electrophysiological studies showing that some V4 cells respond best if the color outside the receptive field is different from the color preferred in the receptive field (Schein and Desimone, 1990). These cells provide a fourth stage of color perception that may be important for color constancy and for discrimination between a figure and background. Additional evidence of the role of V4 in color vision comes from PET studies in humans. Area V4 is activated when subjects view colored stimuli but not when they view black-and-white stimuli (Zeki et al., 1991).

It would probably be wrong to think of area V4 as devoted exclusively to color perception. Cells in V4 are also tuned in the spatial domain, for orientation and for spatial frequency (Desimone and Schein, 1987). Schiller (1993) lesioned V4 in monkeys and found color vision relatively unaffected. V4 is the main pathway between the secondary visual area (V2) and the inferior temporal visual region, and it probably serves several aspects of visual perception.

Most mammalian species have some color vision

In 1942, Gordon Walls concluded from a survey that, among mammals, color vision is by no means widespread, and this conclusion has been repeated in many books and articles. A much more extensive survey by Gerald Jacobs (1993), however, indicates that most mammals have at least some degree of color vision. Although only certain primates have good trichromatic color vision (vision based on three classes of cone photopigments), many mammalian species have dichromatic color vision (based on two classes of cone pigments). Many so-called color-blind humans (actually color-*deficient* humans) have dichromatic vision and can distinguish short-wavelength stimuli (blue) from long-wavelength stimuli (not blue).

On the basis of his survey, Jacobs (1993) suggested that it is better to think of a continuum of color capabilities than to use an all-or-none criterion, and he proposed that four categories cover all mammalian species:

1. *Excellent trichromatic color vision* is found in diurnal primates such as humans and the rhesus monkey (*Macaca mulatta*).
2. *Robust dichromatic color vision* is found in species that have two kinds of cone photopigments and a reasonably large population of cones. Examples of such species are

the dog, the pig, and many male New World monkeys, such as the squirrel monkey (*Saimiri sciureus*) and the marmoset monkey (*Callithrix jaccus*). (The females may be trichromatic as a result of having genes that encode differing long-wavelength cones on their two X chromosomes.)

3. *Feeble dichromatic color vision* occurs in species that have two kinds of cone pigments but have very few cones. Examples are the domestic cat and the coati (*Nasua nasua*).
4. *Minimal color vision* is possessed by species that have only a single kind of cone pigment and that must rely on interactions between rods and cones to discriminate wavelength. Examples are the owl monkey (*Aotes trivirgatus*) and the raccoon (*Procyon lotor*).

When both diurnal and nocturnal species of a given taxonomic family have been tested for color vision (e.g., the coati and the raccoon), the diurnal species (in this case the coati) usually has the better color vision.

Perception of Visual Motion Is Analyzed by a Special System That Includes Cortical Area V5

Some retinal ganglion cells respond preferentially to a certain direction of motion of objects; for example, they may respond to stimuli that move to the left but not to stimuli that move to the right (Barlow and Levick, 1965). Investigators have hypothesized that the direction-selective responses require retinal circuits involving both excitation and inhibition: whereas movement in the preferred direction stimulates excitatory units before inhibitory units, movement in the nonpreferred direction reaches inhibitory units first.

Motion is analyzed by the cortex, partly in regions close to those that control eye movements. All the neurons in area V5 (also called the *medial temporal area*; see Figure 10.19*c*) in the monkey respond to moving visual stimuli, but they do not respond differentially to the wavelength of stimulation. A variety of studies provide converging evidence that area V5 is specialized for the perception of motion and direction of motion. As mentioned previously, PET studies show that moving stimuli, rather than colored stimuli, evoke responses in human area V5.

When monkeys are trained to report the direction of perceived motion, experimental lesions of area V5 impair their performance, at least temporarily (Newsome et al., 1985). If experimenters electrically stimulated an area of V5 that normally responded to stimuli moving up in visual space, the monkeys reported that dots on the screen were moving up even when they were actually moving to the right.

One striking report described a woman who had lost the ability to perceive motion after a stroke that had damaged her area V5 (Zihl et al., 1983). The woman was unable to perceive continuous motion and saw only separate, successive static images. This impairment led to many problems in her daily life. She had difficulty crossing streets because she could not follow the positions of automobiles in motion: "When I'm looking at the car at first, it seems far away. But then when I want to cross the road, suddenly the car is very near." She also complained of difficulties in following conversations because she could not see the movements of speakers' lips. Except for her inability to perceive motion, this woman's visual perception appeared normal.

The Many Cortical Visual Areas Are Organized into Two Major Systems

Many investigators have wondered why primate visual systems contain so many distinct regions. Certain regions specialize in processing different attributes of visual experience (such as shape, location, color, motion, and orientation). But the number of visual fields—over 30—is larger than the number of basic attributes. Perhaps the reason that so many separate visual regions have been found is simply that investigators, being visually oriented primates themselves, have lavished special attention on the visual system.

Earlier work with hamsters led to the hypothesis that there are two visual systems: one, for *identification* of objects, involves especially the visual cortex; the other, for *location* of objects, involves especially the superior colliculus (G. E. Schneider, 1969).

Mortimer Mishkin and Leslie Ungerleider (1982) proposed that primates also have two main cortical processing streams, both originating in primary visual cortex: a ventral processing stream responsible for visually *identifying* objects, and a dorsal stream responsible for appreciating the spatial *location* of objects and visual guidance of movement toward objects (**Figure 10.27**). These processing streams were called, respectively, the *what* and *where* streams.

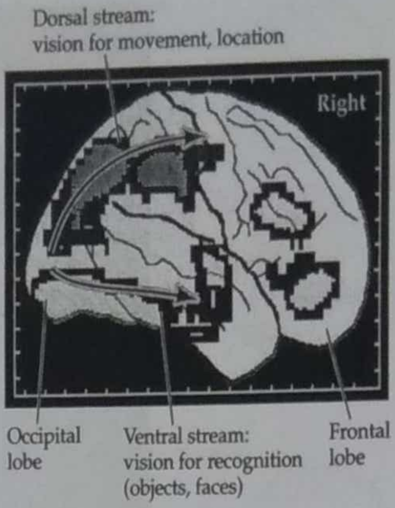
PET studies, as well as brain lesions in patients, indicate that the human brain also possesses *what* and *where* visual processing streams similar to those found in monkeys (Ungerleider et al., 1998). The two streams are not really discrete because there are normally many cross-connections between them. In the ventral stream, including regions of the occipitotemporal, inferior temporal, and inferior frontal areas, information about faces becomes more specific as one proceeds farther forward. PET studies show that, whereas general information about facial features and gender is extracted more posteriorly, the more anterior parts of the stream provide representations of individual faces (Courtney et al., 1996).

Discovery of these separate visual cortical streams helps us understand the case of patient D.F., described at the start of this chapter. Recall that, after carbon monoxide poisoning, she lost the ability to perceive faces and objects while retaining the ability to reach and grasp under visual control. The investigators who studied her (A. D. Milner et al., 1991) hypothesized that D.F.'s ventral visual stream was devastated but that her dorsal stream was unimpaired. An opposite kind of dissociation had already been reported: damage to the posterior parietal cortex often results in optic **ataxia** in which patients have difficulty using vision to reach for and grasp objects, yet some of these patients can still identify objects correctly (Perenin and Vighetto, 1988).

Recent MRI imaging with D.F. supports the interpretation of impairment in her ventral stream but a relatively normal dorsal stream (T. W. James et al., 2003). High-resolution MRI of D.F.'s brain (**Figure 10.28*a***) reveals diffuse damage with a concentration in the ventrolateral occipital cortex. Throughout the brain, there is evidence of atrophy, indicated by shrunken gyri and enlarged sulci.

Figure 10.28*b* shows the area activated in fMRI recordings when normal subjects viewed pictures of objects; it corresponds to D.F.'s lateral occipital lesion. When D.F. reached for and grasped objects, her fMRI activation in the parietal lobe was similar to that of normal subjects, indicating that D.F.'s dorsal stream is largely intact. D.F.'s intact dorsal pathway not only tells her where objects are but also guides her movements to use these objects properly.

It is still puzzling to understand how one part of D.F. knows exactly how to grasp a pencil while another part of her—the part that talks to you—has no idea whether it's a pencil, a ruler, or a bouquet of flowers. Imagining what this disjointed visual experience must be like for D.F. allows us to appreciate how effortlessly our brains usually bind together information to give us the marvelous sense of sight.


Dorsal stream:
vision for movement, location
Right
Occipital lobe
Ventral stream:
vision for recognition (objects, faces)
Frontal lobe

10.27 Parallel Processing Pathways in the Visual System The ventral (*what*) pathway shown in yellow and red, and the dorsal (*where*) pathway shown in green and blue, serve different functions. (Courtesy of Leslie Ungerleider.)

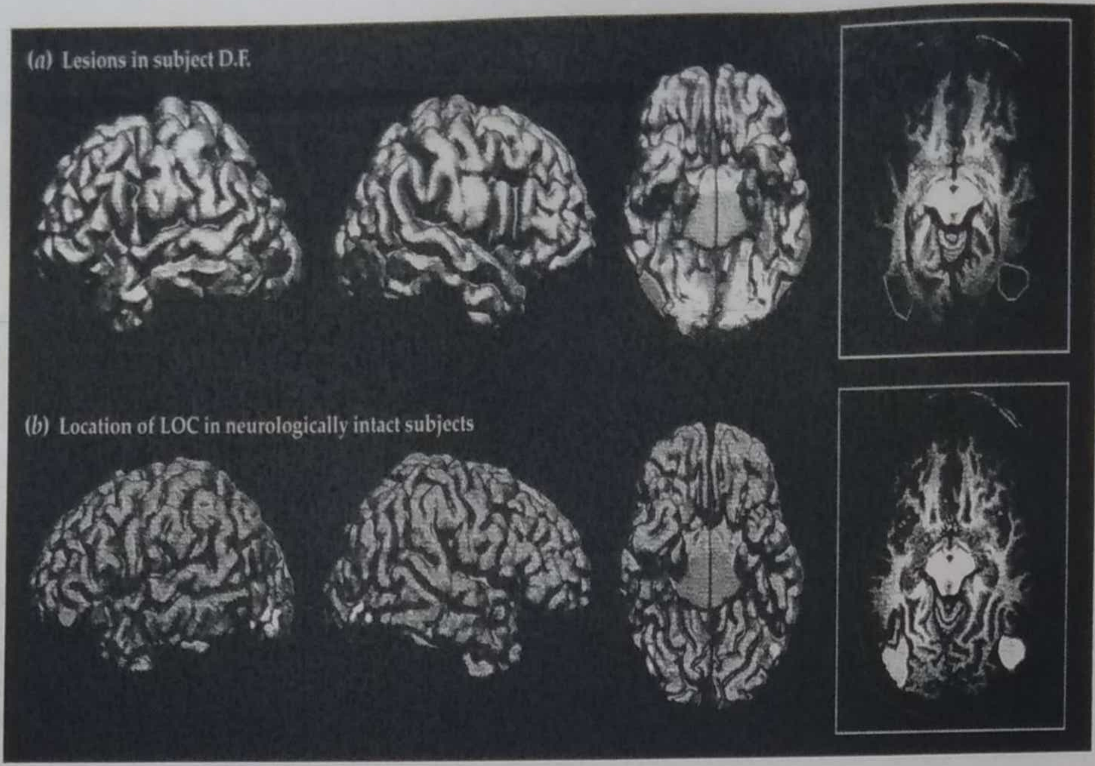
The anterior part of the dorsal stream includes "mirror neurons"

The anterior part of the dorsal visual stream merges with the motor cortex and includes neurons that have both visual and motor functions. These neurons were discovered by investigators who were recording with electrodes implanted in the motor cortex of monkeys. To their surprise, the investigators found cells that fired not only when the monkey grasped and moved an object but also when the monkey observed another monkey or a person grasping and moving an object.

It took the investigators several years to believe and publish their finding (Di Pellegrino et al., 1992). They proposed that these **mirror neurons** mediate the understanding of actions performed by others: when an individual sees an action performed by another, neurons that represent that action are activated in the observer's premotor cor-

ataxia An impairment in the direction, extent, and rate of muscular movement.

mirror neuron A neuron that is active when an individual makes a particular movement, but is also active when that individual sees another individual make that same movement.


(a) Lesions in subject D.F.
(b) Location of LOC in neurologically intact subjects

10.28 Object Recognition Centers in the Brain (a) In this reconstruction from MRI images, the brain region that was damaged in patient D.F. (blue) is seen from lateral views and from below (outlined in orange on the right). (*b*) In neurologically intact subjects, this same brain region is activated (yellow) when the subjects are looking at recognizably intact pictures of various objects rather than scrambled pictures. D.F.'s inability to recognize the objects she sees appears to be due to the damage to this region on the border of the occipital and temporal cortex. (From T. W. James et al., 2003; courtesy Thomas James.)

tex (see Figure 11.17). This automatically induced motor representation of the observed action corresponds to activation that is generated during motor activity and that has an outcome known to the observer. Thus the mirror system transforms visual information into knowledge (Rizzolatti and Craighero, 2004).

Several studies provide data for the existence of a mirror neuron system in humans. For example, it has long been known that EEG activation occurs in the motor region not only during active movement but also when a person observes actions performed by others (Gastaut and Bert, 1954). Further evidence has come from studies using functional MRI while the subject watched actions performed by another human or by an animal (e.g., Buccino et al., 2004). Watching was found to evoke cortical activity in the appropriate region of the motor cortex.

The human mirror neuron system possesses some important properties not observed in the monkey system. First, meaningless movements activate the mirror neuron system in humans but not in monkeys. Second, the temporal characteristics suggest that the human systems code for the component movements of an action, whereas the monkey systems code only for the total action. The investigators suggest that these differences should favor the ability of humans to imitate the actions of others (Rizzolatti and Craighero, 2004, p. 176).

The discovery of mirror neurons has stimulated much research and speculation, so you are likely to see more about them in the future. The mirror neuron system has been related to topics as varied as empathy, learning by imitation, and the evolution of language; impairments of the mirror-neuron system have been proposed as a cause of autism, which is characterized by impairments in understanding other people's behavior. We will consider additional aspects of mirror neurons in Chapter 11 in the context of the motor system.

Visual Neuroscience Can Be Applied to Alleviate Some Visual Deficiencies

Vision is so important that many investigators have sought ways to prevent impairment, to improve inadequate vision, and to restore sight to the blind. In the United States, half a million people are blind. Recent medical advances have reduced some causes of blindness but have increased blindness from other causes. For example, medical advances permit people with diabetes to live longer. But because we don't know how to prevent blindness associated with diabetes, there are more people alive today with diabetes-induced blindness. In the discussion that follows we will first consider ways of avoiding impairment of vision. Then we will take up ways of exercising and training that are designed to improve an impaired visual system.

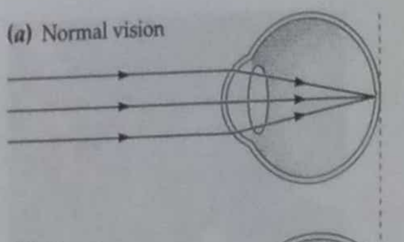
Impairment of vision often can be prevented or reduced

Studies of the development of vision in children and other animals show that the incidence of **myopia** (nearsightedness) (from the Greek *myein*, "to be closed," and *ops*, "eye") can be reduced. Myopia develops if the eyeball is too long, forcing the eye to focus objects in front of the retina rather than on the retina (**Figure 10.29**). As a result, distant objects appear blurred. Considerable evidence suggests that myopia develops when children spend a lot of time looking at targets close up rather than at objects far away (Marzani and Wallman, 1997).

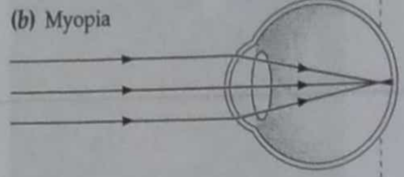
Before civilization, most people spent most of their time looking at objects far away, such as predators, prey, sources of water, and so on. Thus they kept the eye relaxed most of the time. Now, however, people spend long periods of time gazing at objects close at hand, such as books and computer screens. This constant close focusing requires that the lens be kept thick (unrelaxed). The developing eyeball compensates by elongating to make focusing easier, thus causing progressive myopia. The following preventive steps can be taken, especially during childhood and adolescence:

- Read only in adequate light—enough that you can hold the book as far away as possible and still discern the words.
- Avoid small type.
- If you already have a prescription for myopia but you can read without using glasses, do so, because reading with glasses forces you to thicken your lens more, thus accelerating the problem.

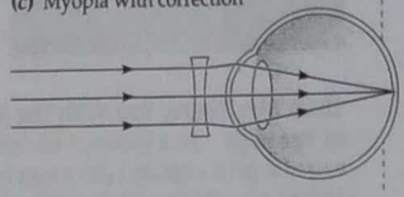
(*a*) Normal vision



(*b*) Myopia



(*c*) Myopia with correction



10.29 Focusing Images on the Retina (*a*) Normally the cornea and lens refract light to focus a sharp image of the outside world on the retina. (*b*) In myopia, the eyeball is too long, so that the image is in focus in front of the retina. In this case, the image that actually reaches the retina is blurred. (*c*) Eyeglasses refract the light before it reaches the cornea to bring the image into sharp focus on the retina.

Increased exercise can restore function to a previously deprived or neglected eye

In Chapter 7 we considered the misalignment of the two eyes (*lazy eye*), which can lead to the condition called **amblyopia** (from the Greek *amblys*, "dull" or "blunt"; and *ops*, "eye"), in which acuity is poor in one eye, even though the eye and retina are normal. If the two eyes are not aligned properly during the first few years of life, the primary visual cortex of the child tends to suppress the information that arrives in the cortex from one eye, and that eye becomes functionally blind. Studies of the development of vision in children and other animals also show that most cases of amblyopia are avoidable.

The balance of the eye muscles can be surgically adjusted to bring the two eyes into better alignment. Alternatively, if the weak eye is given regular practice, with the good eye covered, then vision can be preserved in both eyes. Attempts to alleviate amblyopia by training, however, have produced mixed results and a great deal of controversy. In a study sponsored by the American Academy of Ophthalmology, 507 patients, aged 7 to 17, were assigned at random to one of two groups. The participants in one group were given optimal optical correction. Those in the other group were given not only optical correction but also a patch covering the good eye (**Figure 10.30**), and they participated in visual exercises for 26 weeks. Patients were considered to have improved if, after treatment, they could read two or more lines further down on a standard eye chart. One-fourth of those who received only optical correction showed improvement, but among those who had eye patches and engaged in visual exercises, half improved (Pediatric Eye Disease Investigator Group, 2005).

Other studies have reported considerable improvement, even with adults, if the eye is exercised sufficiently and if the amblyopia is not too severe. A remarkable study by Chow and Stewart (1972) encouraged much subsequent work on rehabilitation, even

myopia Nearsightedness; the inability to focus the retinal image of objects that are far away.

amblyopia Reduced visual acuity that is not caused by optical or retinal impairments.

10.30 Hey There, You With the Stars in Your Eye As a treatment for amblyopia, this girl is wearing a patch over her "good" eye—the one she has been relying upon while ignoring information from her other, "weak" eye. Visual experience through the weak eye will strengthen its influence on the cortex.

in adult people and other animals. Chow and Stewart studied kittens, depriving one or both eyes of pattern vision for about the first 20 months after birth—longer than the critical period for the development of visual function (from about 3 to 12 weeks of age). When a unilaterally deprived kitten was then tested for pattern perception with the previously deprived eye, it showed almost no discrimination on formal tests and it was not able to guide its locomotion visually, although it performed well using its other eye.

The investigators then undertook an intensive program of rehabilitation with some of the kittens. They "gentled" and petted these animals frequently to keep them working on the demanding program. Over time the kittens developed some pattern discrimination with the previously deprived eye, and they could use it to guide their locomotion. Furthermore, recovery of vision was accompanied by morphological changes in the LGN. After monocular deprivation, the LGN cells that had received input from the deprived eye were about one-third smaller than those that had been stimulated by pattern vision. When the previously deprived eye was retrained, the difference in size of LGN cells disappeared. Electrical recording showed that retraining also increased the number of binocular cells (those that respond to stimulation of either eye) in the visual cortex, in comparison with kittens that were not retrained.

Such animal research, as well as research with human patients, provides encouraging examples for programs of rehabilitation (Bach-y-Rita, 1992). In Chapter 7 we saw that Michael May, who was blind from the age of 3 to 43, regained some aspects of vision quickly following surgery to let light back into one of his eyes. Other aspects, such as the perception of faces and objects, remain severely impaired—but nevertheless show improvement with practice.

Most of us can expect our visual acuity to decline steadily, although not severely, after age 40. Recent research suggests that much of this decline is caused by changes in cortical visual pathways (Schmolesky et al., 2000). Investigators measured electrical responses of single neurons in the primary visual cortex of young adult or old macaque monkeys. The neurons of the old monkeys showed increased spontaneous activity and decreased selectivity for the orientation of stimuli, both of which may be caused by age-related degeneration of intracortical inhibition. Might visual exercise counteract these changes?

Frequent causes of visual impairment, especially with age, are diseases such as macular degeneration that damage the rods and cones. These diseases leave the ganglion cells and the higher neural pathways largely intact. Scientists at the Sandia National Laboratories and two universities are working on a 33-by-33 array of electrodes to be placed within the eye in contact with the ganglion cells. These electrodes would be stimulated by a small camera and radio frequency transmitter lodged in the patient's eyeglasses. The researchers hope to begin implanting the electrode array in patients in the next few years. (Note that a resolution of 33 by 33 pixels is, as illustrated in Figures 10.1 and 10.2, enough to recognize a face.) "The aim is to bring a blind person to the point where he or she can read, move around objects in the house, and do basic household chores," says Sandia project leader Kurt Wessendork. "They won't be able to drive cars, at least in the near future, because instead of millions of pixels, they'll see approximately a thousand ... But people who are blind will see" (N. Singer, 2002, p. 1).

Summary

1. The perception of forms and the recognition of objects are complex accomplishments that require processing in many parts of the visual system.
2. The vertebrate eye is an elaborate structure that forms detailed and accurate optical images on the receptive cells of the retina.
3. Many different phyla have independently evolved photoreceptor organs; several have evolved eyes with lenses to focus light.
4. Visual-information processing begins in the retina, where cells that contain photopigments capture light and initiate neural activity. Two kinds of retinal receptor cells—rods and

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.

CHAPTER 11

© The Estate of Keith Haring

Keith Haring, *Untitled*, 1986

CONTENTS

The Behavioral View 321

The Control Systems View 323

The Neuroscience View 324

Movements Are Controlled at Several Nervous System Levels 332

Extrapyramidal Systems Also Modulate Motor Commands 339

Disorders of Muscle, Spinal Cord, or Brain Can Disrupt Movement 342

We Can Trace a Choice Response from Input to Output 350

Motor Control and Plasticity

What You See Is What You Get

Ian Waterman had a perfectly ordinary life until he caught a viral infection at age 19. For reasons that no one understands, the infection targeted a very specific set of nerves sending information from his body to his brain. Ian can still feel pain or deep pressure, as well as warm and cool surfaces on his skin, but he has no sensation of light touch below his neck. What's more, although Ian can still move all of his muscles, he receives no information about muscle activity or body position (Cole, 1995). You might think this wouldn't cause any problem, because you've probably never thought much about your "body sense"; it's not even one of the five senses that people talk about, is it?

In fact, however, the loss of this information was devastating. Ian couldn't walk across a room without falling down, and he couldn't walk up or down stairs. The few other people suffering a loss like this have spent the rest of their lives in wheelchairs. But Ian was a young and determined person, so he started teaching himself how to walk using another source of feedback about his body: his vision. Now, as long as the lights are on, Ian can carefully watch his moving body and gauge what motor commands to send out to keep walking. If the lights go out, however, he collapses, and has learned that he will just have to lie where he is until they come on again. He has so finely honed this ability to guide movements with vision that if asked to point repeatedly to the same point in the air, he does so more accurately than control subjects do. Still, it's a mental drain to have to watch and attend constantly to his body just to do everyday tasks.

Today Ian has a good job and an active, independent life, but he is always vigilant. Lying in bed, he has to be very careful to remain calm, tethering his limbs with the covers to prevent them from flailing about.

And the lights are always on at Ian's house.

Our emphasis in this chapter shifts to the motor system as we complete the circuit from sensory input to behavior. It is important to consider sensory and motor functions together. Just as we saw in Chapters 8 through 10 that motor activities are important for sensory and perceptual functions—movements of the fingers in active touch perception, sniffing in smell, and movements of the eyes and head in vision—so we will see in this chapter that sensory and perceptual processes guide and correct our actions.

In addition, just as our apparently effortless perception turns out to depend on intricate sensory mechanisms and perceptual processes, so, too, our apparently effortless adult motor abilities—such as reaching out and picking up an object, walking across the room, sipping a cup of coffee—require complex muscular systems with constant feedback from the body, as Ian's case shows. After examining movements and their coordination from the behavioral view and control systems view, in this chapter we'll integrate these into the neuroscience view.

The Behavioral View

By the early nineteenth century, scientists knew that the dorsal roots of the spinal cord serve sensory functions and that the ventral roots contain motor fibers; connections between the two seemed to provide the basis for simple movements. British physiologist Charles Sherrington conducted extensive studies of **spinal animals** (animals in which

spinal animal An animal whose spinal cord has been surgically disconnected from the brain to enable the study of behaviors that do not require brain control.

reflex A simple, highly stereotyped, and unlearned response to a particular stimulus (e.g., an eye blink in response to a puff of air).

movement A brief, unitary activity of a muscle or body part, less complex than an act.

act Also called *action pattern*. Complex behavior, as distinct from a simple movement.

motor plan Also called *motor program*. A plan for action in the nervous system.

the spinal cord has been disconnected from the brain). He showed that skin stimulation, such as pinching, provokes simple acts such as limb withdrawal. Many such observations led him to argue that the basic units of movement are **reflexes**, which he defined as simple, highly stereotyped, and unlearned responses to external stimuli. We analyzed the famous knee jerk reflex in Figure 3.14.

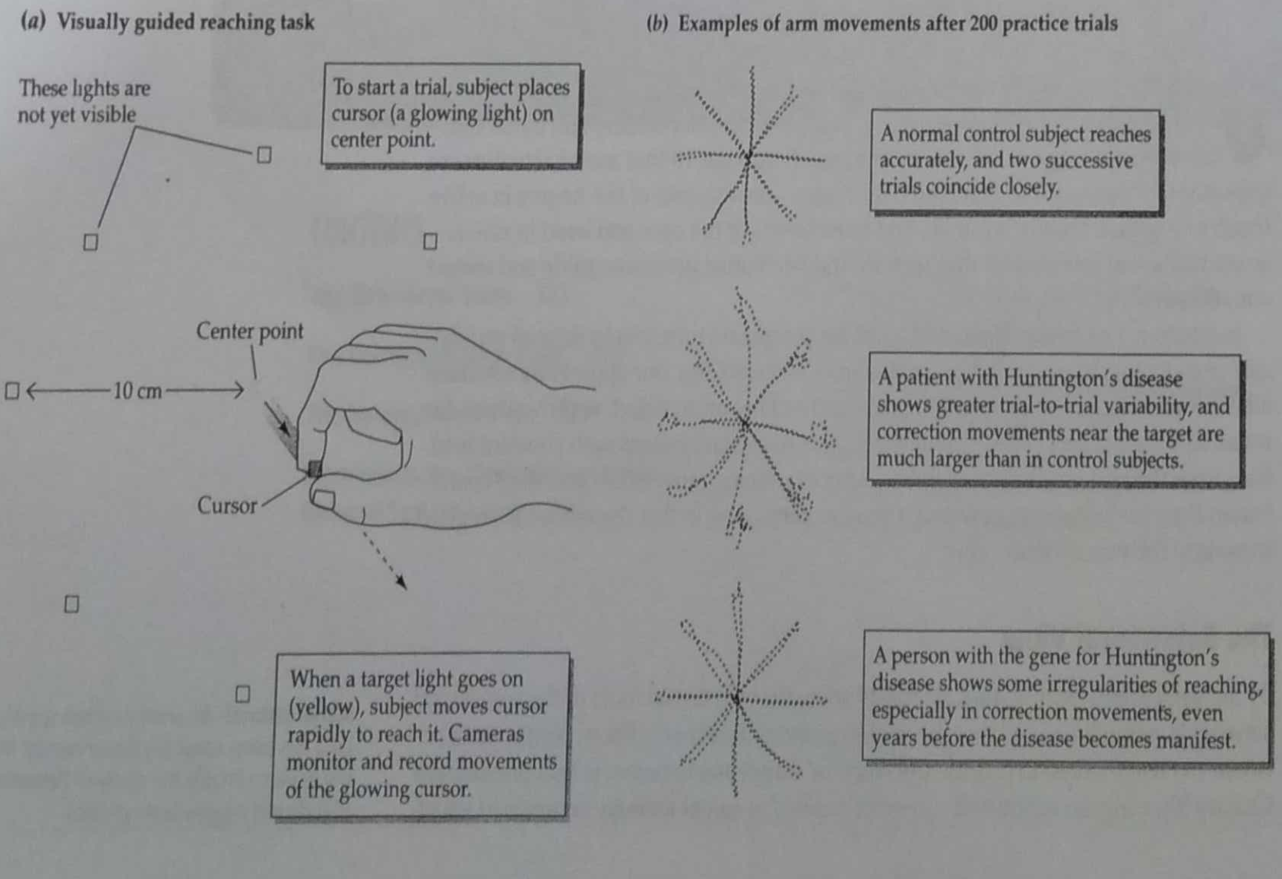
Sherrington's work provoked a rush to identify various reflexes and their pathways in the nervous system, particularly in the spinal cord. These studies showed that some reflexes involve only short pathways in the spinal cord linking dorsal and ventral roots; others involve longer loops connecting spinal cord segments to each other, or to brain regions.

Simple reflexes include brief, unitary activities of muscle called **movements**. Movements are discrete, in many cases limited to a single part of the body, such as a limb. In contrast, complex, sequential behaviors such as putting on a jacket are considered **acts**, or *action patterns*. Different movements of several body parts might be included in such behaviors. You can think of an act as being made up of a particular sequence of movements.

So, are acts simply the connecting together of different reflexes, the sensation from one reflex triggering the next? The limitations of this perspective are apparent when we think about complex sequences of behavior, such as speech, in reflex terms. For example, is speech a set of reflexes in which the movements and sounds associated with each speech element provide the stimuli for the next element? No. A speaker has a *plan* in which several units (speech sounds and words) are placed in a larger pattern. Sometimes the units are misplaced, although the pattern is preserved: "Our queer old dean," said history professor William Spooner, when he meant, "Our dear old queen." Or "You hissed all my mystery lectures." (Spooner was so prone to mixing up the order of sounds in his sentences that this type of error is called a *spoonerism*.) Such mistakes reveal a plan: the speaker is *anticipating* a later sound and executing it too soon. A chain of reflexes would not make such an error.

The **motor plan**, or *motor program*, is a complex set of commands to muscles that is completely established before an act occurs. Feedback from movements informs and

11.1 Measurement of Reaching Movements (*a*) An experimental setup to study reaching movements. (*b*) Recorded movement trajectories of a normal subject (*top*), a patient with Huntington's disease (*middle*), and a carrier of the gene for Huntington's disease (*bottom*). We'll discuss this disorder in detail later in this chapter. (Part *b* courtesy of Maurice R. Smith.)



(*a*) Visually guided reaching task

(*b*) Examples of arm movements after 200 practice trials

These lights are not yet visible

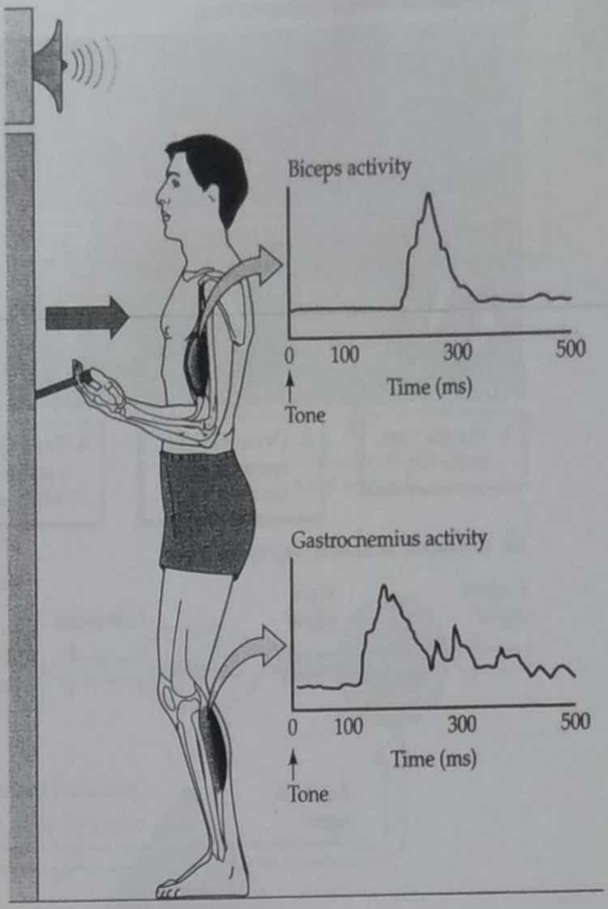
To start a trial, subject places cursor (a glowing light) on center point.

When a target light goes on (yellow), subject moves cursor rapidly to reach it. Cameras monitor and record movements of the glowing cursor.

A normal control subject reaches accurately, and two successive trials coincide closely.

A patient with Huntington's disease shows greater trial-to-trial variability, and correction movements near the target are much larger than in control subjects.

A person with the gene for Huntington's disease shows some irregularities of reaching, especially in correction movements, even years before the disease becomes manifest.



11.2 Electromyography For these recordings made from biceps and gastrocnemius (calf) muscles, the subject was instructed to pull the handle as soon as a tone sounded. (After Purves et al., 2001.)

fine-tunes the motor program as the execution is unfolding, but the basic sequence of movements was planned. Examples of behaviors that exhibit this kind of internal plan range from highly skilled acts, such as piano playing, to a wide repertoire of simple escape behaviors of animals such as crayfish.

Movements and acts can be analyzed and measured in a variety of ways

Movements and acts are readily visible in motion pictures, and high-speed photography provides an intimate portrait of even the most rapid events. To deal with the large amounts of data furnished by high-speed photography, methods of simplification or numerical analysis have been devised. For example, sports trainers use detailed analyses of athletic acts based on time-lapse photographs or information derived from sensors attached at joints. Computer programs process digital photos to help quantify the performance, enabling detailed measurement of the positions of different body parts in successive instants. Other devices record the direction, strength, and speed of motions. **Figure 11.1** illustrates the paths of normal and impaired reaching movements, a kind of movement considered at several points in this chapter.

Another approach to the fine-grained analysis of movements is to record the electrical activity of muscles—a procedure called **electromyography (EMG)**. Like neurons, muscles produce action potentials when they contract, as we'll see later in this chapter. Therefore, fine needle electrodes placed in a muscle, or electrodes placed on the skin over a muscle, can detect electrical indications of muscle activity (**Figure 11.2**). If electrodes are placed over several different muscles, we get a record of the contraction of the muscles involved in an act, including the progressive buildup and decay of their activity (Hanakawa et al., 2003). The EMGs in Figure 11.2 show that a person pulling a knob will adjust his legs just before moving his arm—another example of motor planning.

The Control Systems View

Engineering descriptions of the regulation and control of machines provide a useful look at the mechanisms that regulate and control our movements. In designing machines, engineers commonly have two goals: (1) accuracy, to prevent or minimize error; and (2) speed, to accomplish a task quickly and efficiently. Usually it is difficult to pursue one of these goals without neglecting the other. Two forms of control mechanisms—closed-loop and open-loop—are commonly employed to optimize performance according to these criteria.

Closed-loop control mechanisms maximize *accuracy*: information from whatever is being controlled flows back to the device that controls it. Driving a car is an example of a closed-loop motor system; in this case the variable being controlled is the position of an automobile on the road (**Figure 11.3**). Continuous information is provided by the driver's visual system, which guides corrections. Slow, sustained movements, sometimes called **ramp movements** (or *smooth movements*) are usually closed-loop in character, continuously guided by feedback.

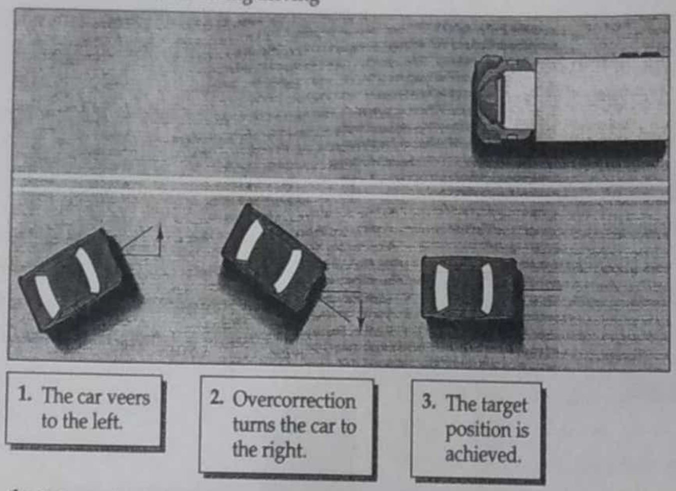
The only way the car could stay on the road without feedback control (e.g., if you were driving with your eyes closed) would be with the aid of accurate memory of all the

electromyography (EMG) The electrical recording of muscle activity.

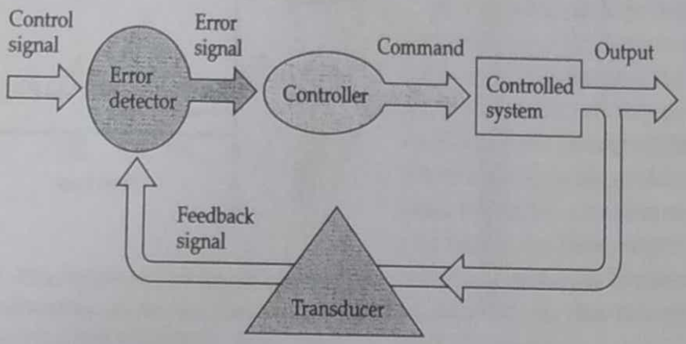
closed-loop control mechanism A control mechanism that provides a flow of information from whatever is being controlled to the device that controls it.

ramp movement Also called *smooth movement*. A slow, sustained motion which is often controlled by the basal ganglia.

(a) Feedback control during driving


1. The car veers to the left.
2. Overcorrection turns the car to the right.
3. The target position is achieved.

(b) Schematic of closed-loop system



11.3 A Closed-Loop System (a) Automobile driving provides an example of feedback control. (b) In the example in part a, the *controlled system* is the automobile. The input to the controlled system (i.e., the *control signal*) is the position of the steering wheel; the *output* is the position of the car on the road. In any closed-loop system, the transducer is an element that measures output, and the error detector measures differences between actual output and desired output (the control signal). In this example the *transducer* (the visual system), the *error detector* (the perceptual system), and the *controller* (the muscles) are all properties of the person driving the car. The driver compares the actual position of the car with its desired position on the road and makes corrections to minimize the discrepancy. Closed-loop systems emphasize accuracy and flexibility at the expense of speed.

turns and bends in the road. But the car would not be able to deal with anything new, such as other moving cars. Such a memory system could be considered a form of open-loop control.

Open-loop control mechanisms maximize *speed;* there are no external forms of feedback, and the activity is preprogrammed. Open-loop controls are needed in systems that must respond so rapidly that there is no time to wait for a feedback pathway. For example, once a baseball pitcher begins throwing a fastball, the pitch will be completed no matter what sensory feedback is received. Such open-loop movements are called **ballistic movements.** Because there is no feedback, open-loop systems need other ways to reduce error and variability. They must anticipate potential error. As living systems, we learn how to accurately anticipate and avoid error when executing a rapid sequence of movements.

Most of our movements represent a blending of these two types of systems: preprogrammed sequences of movements (open-loop) that are fine-tuned by sensory feedback (closed-loop).

The Neuroscience View

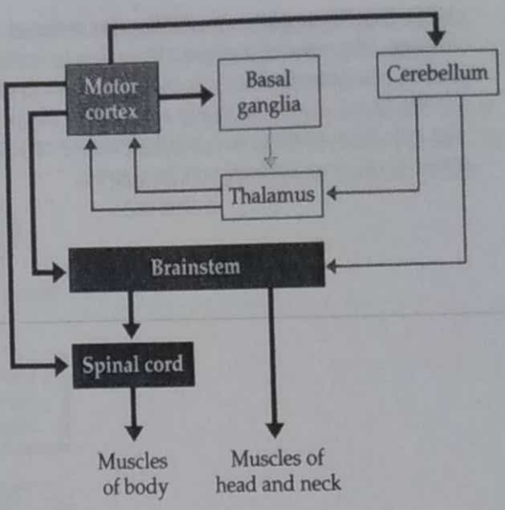
We can distinguish several different levels of hierarchically organized motor control systems:

- The *skeletal system* and the muscles attached to it determine which movements are possible.
- The *spinal cord* controls skeletal muscles in response to sensory information. In the simplest case, the response may be a reflex. The spinal cord also implements motor commands from the brain.
- The *brainstem* integrates motor commands from higher levels of the brain and transmits them to the spinal cord. It also relays sensory information about the body from the spinal cord to the forebrain.
- Some of the main commands for action are initiated in the *primary motor cortex.*
- Areas adjacent to the primary motor cortex, *nonprimary motor cortex,* initiate another level of cortical processing.
- Other brain regions—the *cerebellum* and *basal ganglia*—modulate the activities of these hierarchically organized control systems.

We will examine each of these levels of control in more detail. This organizational scheme, outlined in **Figure 11.4**, will guide the discussion.

open-loop control mechanism A control mechanism in which feedback from the output of the system is not provided to the input control.

ballistic movement A rapid muscular movement which is often organized or programmed in the cerebellum.



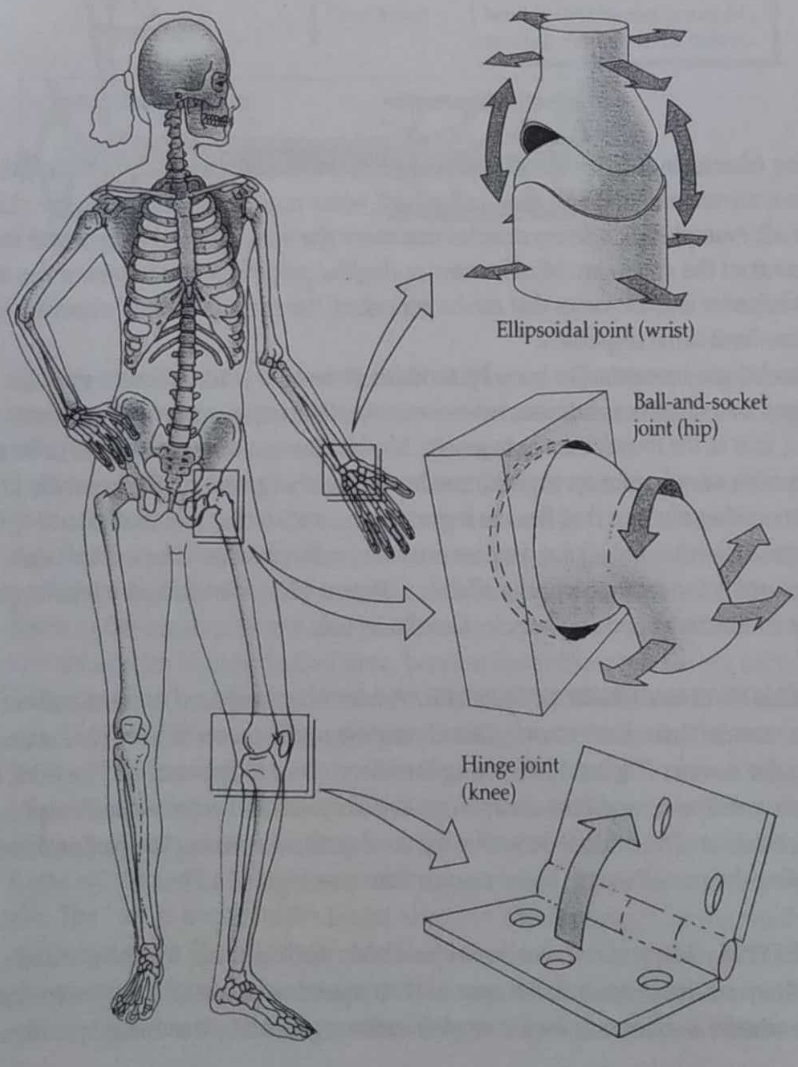
11.4 The Hierarchy of Movement Control The motor cortex receives information from other cortical areas and sends commands to the thalamus and brainstem, which pass commands to the spinal cord. Both the cerebellum and the basal ganglia adjust these commands.

The skeletal system enables particular movements and precludes others

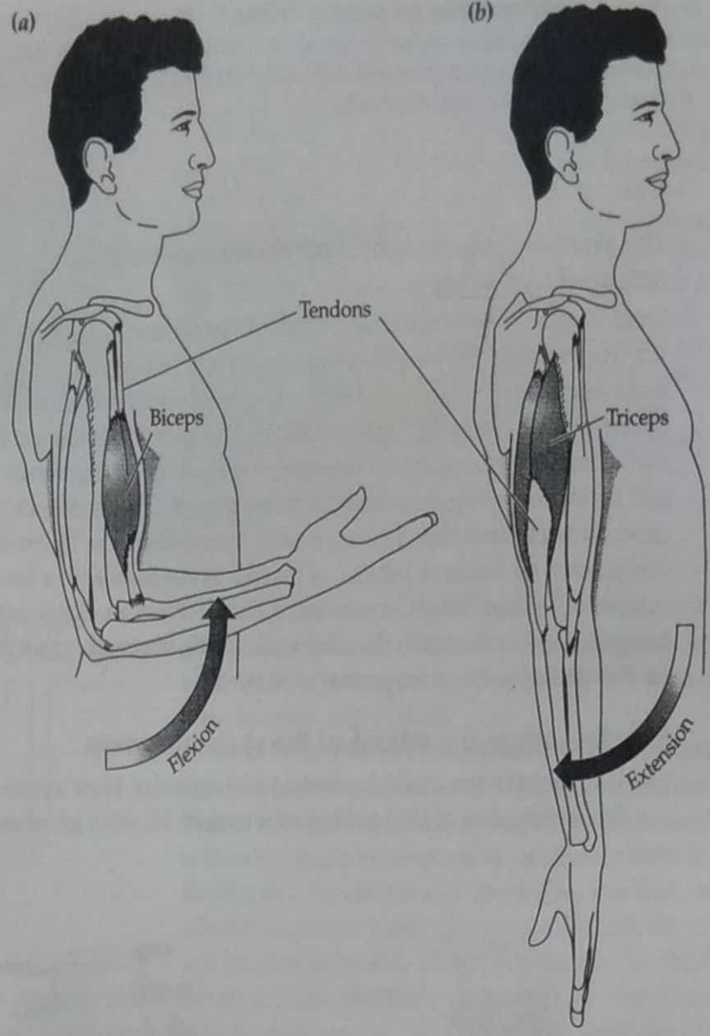
Some properties of behavior arise from physical characteristics of the skeleton. For example, the length, form, and weight of the limbs shape an animal's stride. The primary sites for bending are the joints, where bones meet. **Figure 11.5** illustrates the human skeleton and shows examples of joints and their possible movements. Some joints, such as the hip, are almost "universal" joints, permitting movement in many planes. Others, like the elbow or knee, are more limited and swing mostly in one direction. Interestingly, the octopus has no bones or joints, yet when it grabs food with a tentacle, the octopus will place "bends" in the tentacle as if it had an elbow and wrist to bring the food to its mouth (Sumbre et al., 2005), suggesting that joints may be the optimal solution for precise movements.

Muscles control the actions of the skeletal system

Our bare skeleton must now be clothed with muscles. How a muscle attaches to bones is a direct indication of the movement it causes. Muscles generate force only by con-



11.5 Joints and Movements Enlarged mechanical models indicate the kinds of movements that each type of joint can perform. The wrist joint moves in two principal planes: lateral and vertical. The hip joint is a "universal" joint, moving in all three planes. The knee joint has a single plane of motion.



11.6 The Arrangement of Muscles around the Elbow Because muscles exert force only by contracting, muscle attachments determine the resulting movement. (a) The biceps muscle flexes the arm. (b) The triceps extends the arm. Because these two muscles mediate opposite movements, they are known as *antagonists*.

tracting (shortening). Some muscles produce forces that maintain body posture; others produce movement around a joint. In contrast, some muscles do not act on the skeleton at all; examples include the muscles that move the eyes, lips, and tongue and those that contract the abdomen. Muscles have springlike properties that influence the timing of behavior and the forces that can be generated; the rate and force of muscular contractions limit some responses.

Muscles are connected to bone by **tendons**. Around a joint, different muscles are arranged in a reciprocal fashion: when one muscle group contracts, the other is extended; that is, the muscles are **antagonists**. Muscles that act together are said to be **synergists**. For example, four synergistic muscles act together to extend the leg at the knee. The three other muscles that flex the leg are antagonists to the four that extend it. Coordinated action around a joint requires one set of motoneurons to be excited while the antagonistic set of motoneurons is inhibited (**Figure 11.6**). We can lock a limb in position by contracting opposing muscles simultaneously.

THE MOLECULAR MACHINERY OF MUSCLES A muscle is composed of thousands of individual **muscle fibers**. Each muscle fiber contains many filaments of two kinds arranged in a regular manner (**Figure 11.7**), giving the fibers a striped appearance. The thick and thin filaments (made up of the complex proteins **myosin** and **actin**, respectively) overlap. Contraction of the muscle increases the overlap: the filaments slide past each other, shortening the overall length of the muscle fiber (see Figure 11.7).

MUSCLE TYPES Many of the muscles in your body, such as those in your stomach, are not under your direct control. Because of their appearance, these muscles are called **smooth muscle**, and because their contractions are regulated by the autonomic nervous

tendon Strong tissue that connects muscles to bone.

antagonist A muscle that counteracts the effect of another muscle.

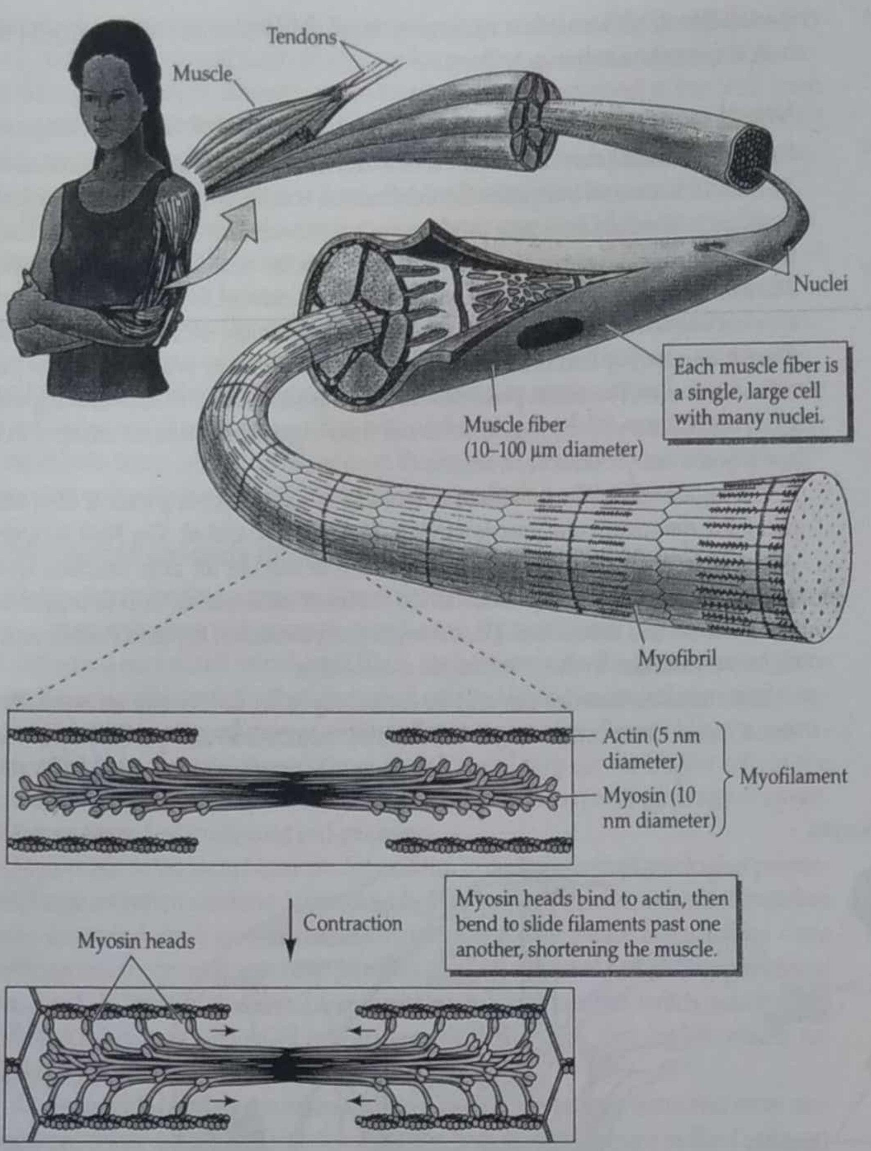
synergist A muscle that acts together with another muscle.

muscle fiber Large, cylindrical cells, making up most of a muscle, that can contract in response to neurotransmitter released from a motoneuron.

myosin A protein that, along with actin, mediates the contraction of muscle fibers.

actin A protein that, along with myosin, mediates the contraction of muscle fibers.

smooth muscle A type of muscle fiber, as in the heart, that is controlled by the autonomic nervous system rather than by voluntary control.


Tendons
Muscle
Nuclei
Each muscle fiber is a single, large cell with many nuclei.
Muscle fiber (10–100 µm diameter)
Myofibril
Actin (5 nm diameter)
Myosin (10 nm diameter)
Myofilament
Contraction
Myosin heads
Myosin heads bind to actin, then bend to slide filaments past one another, shortening the muscle.

11.7 The Composition of Muscles and the Mechanism of Muscle Contraction Muscle fibers are shown here at progressively greater magnifications, from life size to 2 million times life size. The actions of myosin and actin cause muscle contraction.

system, we will not discuss them further. Rather, we will concern ourselves with a second class of muscle, called **striated muscles** (because they have a striped appearance), which are under voluntary control.

Because of the varying tasks they perform, different muscles require different speeds, precision, strength, and endurance. So there are two main types of striated muscle fibers: fast-twitch and slow-twitch. Eye movements, for example, must be quick and accurate so that we can follow moving objects and shift our gaze from one target to another. But fibers in the extraocular muscles, which control eye movements, do not have to maintain tension for long periods of time, because some fibers relax while others contract. The extraocular muscles are therefore made up of **fast-twitch muscle fibers**. In leg muscles, fast-twitch fibers react promptly and strongly but tire rapidly; they are used mainly for activities in which muscle tension changes frequently, as in walking or running. Mixed in with the fast-twitch muscle fibers are **slow-twitch muscle fibers**, which are not as fast but have greater resistance to fatigue; they are used chiefly to maintain posture. If you eat chicken or turkey you've already contrasted fast-twitch and slow-twitch muscles. The "white meats" of the breast were fast-twitch muscles for the rapid wing beats needed for flight. These birds fly only for short periods, so there's no need for these muscles to resist fatigue. In contrast, the "dark meats" of the leg are slow-twitch muscles, which supported the animals continuously as they walked about. These muscles con-

striated muscle A type of muscle with a striped appearance, generally under voluntary control.

fast-twitch muscle fiber A type of striated muscle that contracts rapidly but fatigues readily.

slow-twitch muscle fiber A type of striated muscle fiber that contracts slowly but does not fatigue readily.

motoneuron Also called *motor neuron*. A nerve cell in the spinal cord that transmits motor messages from the spinal cord to muscles.

acetylcholine (ACh) An amine transmitter that stimulates muscle contraction, but is also found throughout the brain.

neuromuscular junction (NMJ) The region where the motoneuron terminal and the adjoining muscle fiber meet; the point where the nerve transmits its message to the muscle fiber.

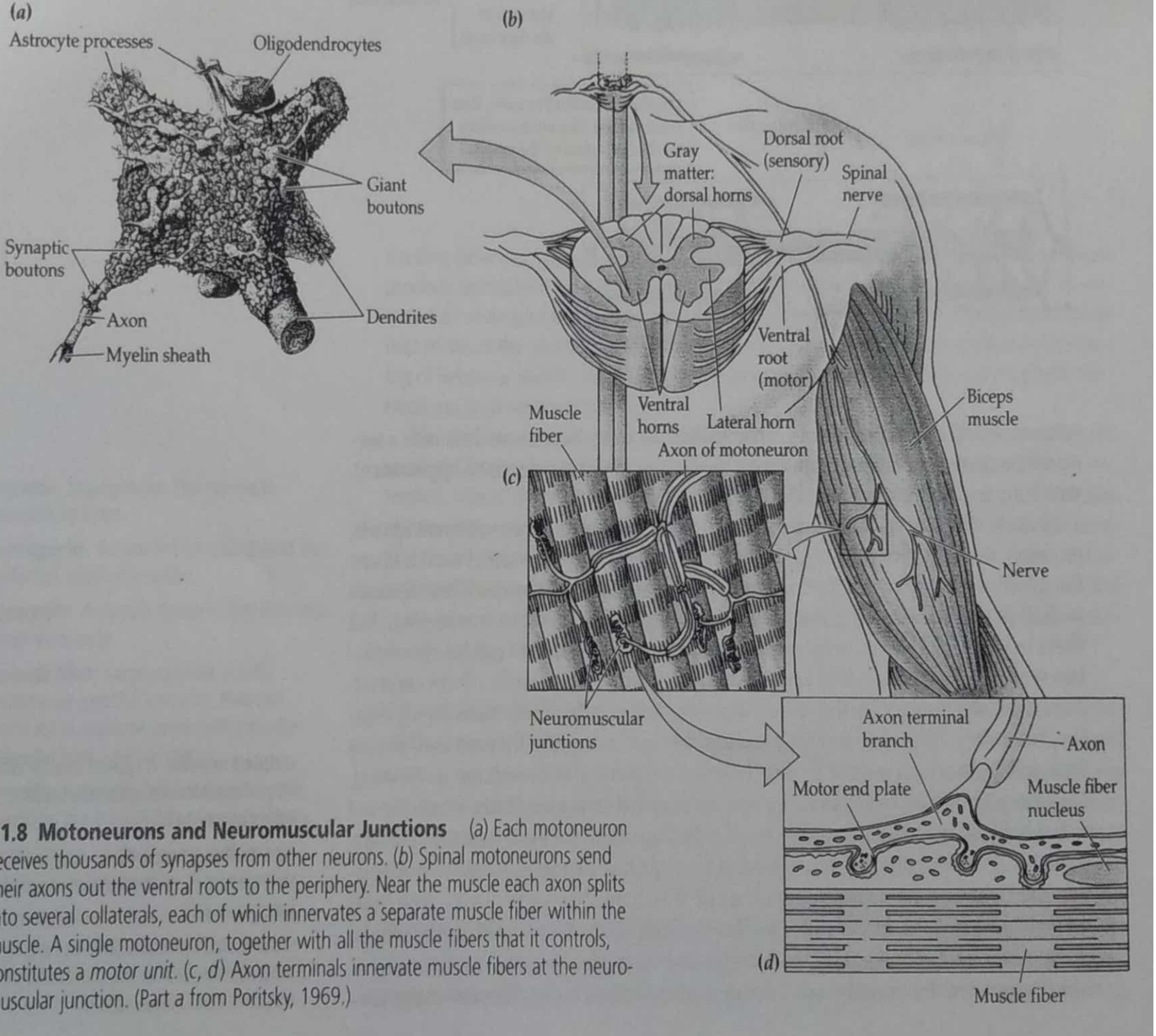
tracted slowly but had lots of endurance. Most muscles consist of a mixture of slow-twitch and fast-twitch muscle fibers.

Neural messages reach muscle fibers at the neuromuscular junction

Recall that neurons that send their axons to innervate muscles are called **motoneurons**. As each motoneuron integrates the information bombarding it through hundreds or thousands of synapses, it may produce an action potential. The action potential will travel down the axon, which splits into many branches near the target muscle (**Figure 11.8*a* and *b***). Each axonal branch carries an action potential to its terminal, which then (in vertebrates) releases the neurotransmitter **acetylcholine (ACh)**. Then all the muscle fibers innervated by that motoneuron respond to the ACh by producing action potentials of their own. The action potentials travel along each muscle fiber, permitting sodium (Na^+) and calcium (Ca^{2+}) ions to enter and then trigger the molecular changes in actin and myosin that produce contraction.

The region where the motoneuron terminal and the adjoining muscle fiber meet is called the **neuromuscular junction (NMJ)** (**Figure 11.8*c* and *d***). The NMJ is large and very effective: almost every action potential that reaches an axon terminal releases enough ACh to cause a depolarization in the innervated muscle fiber to trigger an action potential and contraction. Thus, every action potential in the motoneuron normally elicits a contraction in the postsynaptic muscle fiber.

In vertebrates, muscles can only be excited (by ACh), so the way we normally prevent a muscle from contracting is to inhibit its motoneuron and prevent it from send-


(a)
Astrocyte processes
Oligodendrocytes
Giant boutons
Synaptic boutons
Axon
Myelin sheath
Dendrites
(b)
Gray matter: dorsal horns
Dorsal root (sensory)
Spinal nerve
Ventral root (motor)
Muscle fiber
Ventral horns
Lateral horn
Axon of motoneuron
Biceps muscle
Nerve
(c)
Neuromuscular junctions
Axon terminal branch
Axon
Motor end plate
Muscle fiber nucleus
(d)
Muscle fiber

11.8 Motoneurons and Neuromuscular Junctions (*a*) Each motoneuron receives thousands of synapses from other neurons. (*b*) Spinal motoneurons send their axons out the ventral roots to the periphery. Near the muscle each axon splits into several collaterals, each of which innervates a separate muscle fiber within the muscle. A single motoneuron, together with all the muscle fibers that it controls, constitutes a *motor unit*. (*c*, *d*) Axon terminals innervate muscle fibers at the neuromuscular junction. (Part *a* from Poritsky, 1969.)

ing an action potential to the NMJ. Because it is large and accessible, the NMJ is a very well studied synapse, and much of what we know about synapses and synaptic plasticity (change in synaptic strength across time) was first established at the NMJ. Even though the NMJ is a large and reliable synapse, its properties can change with use. All of us are familiar with muscle fatigue from extended use; some of the reduced responsiveness of the fatigued muscle is due to the diminished effectiveness of NMJs.

The **motor unit** consists of a single motoneuron's axon and all the muscle fibers innervated by its various branches (see Figure 11.8*b*). When the motoneuron fires, each of the muscle fibers that it innervates is stimulated. The **innervation ratio** is the number of muscle fibers innervated by one motor axon. Low innervation ratios characterize delicate muscles involved in fine movements, like those that move the eye—one motoneuron for every three fibers (a 1:3 ratio). Muscles that act on massive muscles such as those of the leg have high innervation ratios, with each motoneuron innervating several hundred muscle fibers (about 1:300), or even thousands of muscle fibers, so a single motoneuron contracts many muscle fibers at once, producing a lot of force.

Motoneurons integrate information from the brain and spinal cord

Muscles contract because motoneurons of the spinal cord and cranial nerve nuclei send action potentials along their axons to muscles (see Figures 2.9 and 2.10 for the anatomy of the cranial nerves and spinal cord). Thus, motoneurons are the **final common pathway**: the sole route through which the spinal cord and brain can control our many muscles. Because they respond to inputs from so many sources (see Figure 11.8*a*), motoneurons often have very widespread dendritic fields, and they are the largest cells in the spinal cord. Furthermore, motoneurons must respond to a tremendous variety of synaptic transmitters, both excitatory and inhibitory.

Motor cells of the spinal cord are not uniform in size or electrophysiological properties. Large motoneurons have axons of wide diameter and therefore conduct impulses faster. In general, small motoneurons innervate slow-twitch muscle fibers and are more easily excited by synaptic currents; therefore they are activated before large motoneurons are (K. E. Jones et al., 1994). Large motoneurons innervate fast-twitch muscle fibers and tend to respond after small cells do because, being large, they are less readily excited by synaptic currents.

As we steadily increase the contraction in a muscle, we activate more and more motoneurons (Henneman, 1991). In doing this, we recruit motoneurons in fixed order according to their size. Weak contraction activates only small, low-threshold neurons for the slow-twitch muscle fibers defined earlier. Stronger stimulation excites larger, higher-threshold neurons that control fast-twitch muscle fibers. This systematic, orderly recruitment of motoneurons based on their size is known as the **size principle**.

Sensory feedback from muscles, tendons, and joints monitors movements

To produce rapid coordinated movements of the body, the integrative mechanisms of the brain and spinal cord must continuously gather information about the state of the muscles, the positions of the limbs, and the instructions being issued by the motor centers. This collecting of information about body movements and positions is called **proprioception** (from the Latin *proprius*, "own," and *recipere*, "to receive"). Because it is crucial for coordinating movement, this information is transmitted to the brain by large, myelinated axons, which conduct action potentials swiftly (see Chapter 3). For some reason, the virus that attacked Ian, whom we met at the start of this chapter, killed only these large axons, leaving him without proprioception below the neck. His predicament illustrates how important this "sixth sense" is for movement.

Two major kinds of proprioceptive receptors that report the state of muscles and joints to the brain are muscle spindles and Golgi tendon organs. We'll discuss each in turn.

THE MUSCLE SPINDLE The **muscle spindle** of vertebrates is a complicated structure consisting of both afferent and efferent elements. The spindle gets its name from its shape: a sort of cylinder that is thicker in the middle and tapers at its two ends. The Latin for

motor unit A single motor axon and all the muscle fibers that it innervates.

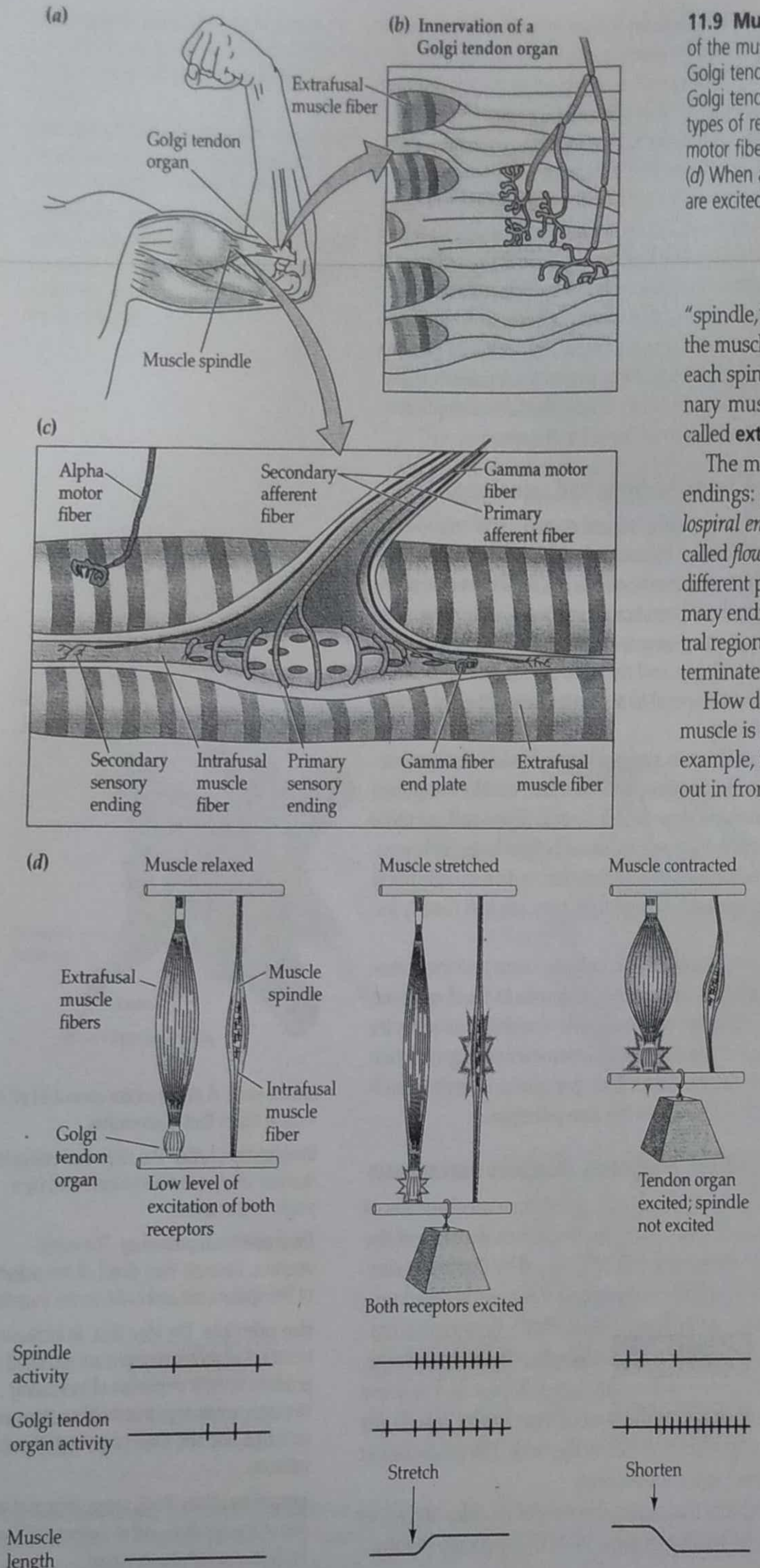
innervation ratio The ratio expressing the number of muscle fibers innervated by a single motor axon.

final common pathway The motoneurons, because they direct all the activity of the spinal cord and brain to the muscles.

size principle The idea that, as increasing numbers of motor neurons are recruited to produce muscle responses of increasing strength, small, low-threshold neurons are recruited first and then large, high-threshold neurons.

proprioception Body sense; information about the position and movement of the body that is sent to the brain.

muscle spindle A muscle receptor that lies parallel to a muscle and sends impulses to the central nervous system when the muscle is stretched.


(a)
Extrafusal muscle fiber
Golgi tendon organ
Muscle spindle
(b) Innervation of a Golgi tendon organ
(c)
Alpha motor fiber
Secondary afferent fiber
Gamma motor fiber
Primary afferent fiber
Secondary sensory ending
Intrafusal muscle fiber
Primary sensory ending
Gamma fiber end plate
Extrafusal muscle fiber
(d)
Muscle relaxed
Muscle stretched
Muscle contracted
Extrafusal muscle fibers
Muscle spindle
Intrafusal muscle fiber
Golgi tendon organ
Low level of excitation of both receptors
Both receptors excited
Tendon organ excited; spindle not excited
Spindle activity
Golgi tendon organ activity
Stretch
Shorten
Muscle length

11.9 Muscle Receptors (*a*) The receptors in the body of the muscle are muscle spindles; those in the tendons are Golgi tendon organs. (*b*) This sensory ending is typical of a Golgi tendon organ. (*c*) A typical muscle spindle has two types of receptor endings: primary and secondary. Gamma motor fibers control a contractile portion of the spindle. (*d*) When a load is imposed on the muscle, muscle receptors are excited as shown here.

"spindle," *fusus*, is used to form adjectives referring to the muscle spindle; thus the small muscle fibers within each spindle are called **intrafusal fibers**, and the ordinary muscle fibers that lie outside the spindles are called **extrafusal fibers (Figure 11.9*a* and *c*)**.

The muscle spindle contains two kinds of receptor endings: **primary sensory endings** (also called *annulospiral endings*) and **secondary sensory endings** (also called *flower spray endings*). These endings are related to different parts of the spindle (see Figure 11.9*c*). The primary ending wraps in a spiral fashion around the central region of the intrafusal fiber. The secondary endings terminate toward the thin ends of the spindle.

How do these elements become excited? Suppose a muscle is stretched, as when a load is placed on it. For example, if you were trying to hold your arm straight out in front of you, palm up, and someone put a book in your hand, that would put an additional load on your arm. Your arm would move down briefly, stretching the biceps muscle. The muscle spindle would also stretch, and the resulting deformation of the endings on the spindle would trigger nerve impulses in the afferent fibers. These afferents would inform the spinal cord, and the spinal cord would tell the brain about the muscle stretch and therefore the load imposed (**Figure 11.9*d***).

intrafusal fiber One of the small muscle fibers that lie within each muscle spindle.

extrafusal fiber One of the ordinary muscle fibers that lie outside the spindles and provide most of the force for muscle contraction.

primary sensory ending Also called *annulospiral ending*. The axon that transmits information from the central portion of a muscle spindle.

secondary sensory ending Also called *flower spray ending*. The axon transmitting information from the ends of a muscle spindle.

Two important factors affect the stretch of the muscle. One is the rate of change of muscle length. In our example the rate of change is jointly a function of the weight of the load and the rate at which the load is applied. The second factor is the force you must continually exert with the muscle to prevent dropping the load. In our example this force is a function only of the weight of the book.

The different receptor elements of the muscle spindle are differentially sensitive to these two features of muscle length changes. The primary (central) endings show a maximum discharge early in stretch and then adapt to a lower discharge rate. In contrast, the secondary endings are maximally sensitive to maintained length and are slow to change their rate during the early phase of stretch. Because of this differential sensitivity, the primary endings are called *dynamic* and the secondary endings are called *static* indicators of muscle length. This distinction arises from the difference in how these receptors are embedded in the spindle rather than from a difference in the nerve fibers themselves.

REGULATION OF MUSCLE SPINDLE SENSITIVITY Muscle spindles not only help maintain posture; they also coordinate movement. A spindle is informed of planned and ongoing actions through innervation by a special motoneuron that alters the tension within the spindle and thus controls the sensitivity of its receptors. These motoneurons are called **gamma motoneurons**, or *gamma efferents*, to distinguish them from the faster-conducting **alpha motoneurons**, which go to the extrafusal muscle fibers that do all the work (see Figure 11.9*c*). The cell bodies of gamma motoneurons are found in the ventral horns of the spinal cord mixed in with the alpha motoneurons.

The gamma motoneuron axon fibers connect to a contractile region of the spindle. Activity in the gamma fibers causes a contraction in the length of the spindle, which modifies its sensitivity to changes in the length of adjacent extrafusal muscle fibers. Hence the number of impulses elicited in the spindle afferents is a function of two factors: (1) muscle stretch and (2) the resting tension in the muscle spindle.

How do the gamma motoneurons help coordinate movements? Suppose that instead of continuing to hold your arm out straight ahead, you move your forearm up and down. If the muscle spindle had only one fixed degree of internal tension, it would not be able to help monitor and coordinate this movement.

As the forearm moves up, both the extrafusal and the intrafusal fibers shorten. Shortening the spindle, as we have noted, removes the tension, so the sensory endings should no longer respond. But the real situation is more complicated and more effective: as the muscle shortens, the gamma efferents correspondingly increase the tension on the intrafusal fibers to maintain their sensitivity. One reflection of the importance of the gamma efferent system is the fact that about 30% of all efferent fibers are gamma motoneurons (the rest are alpha motoneurons).

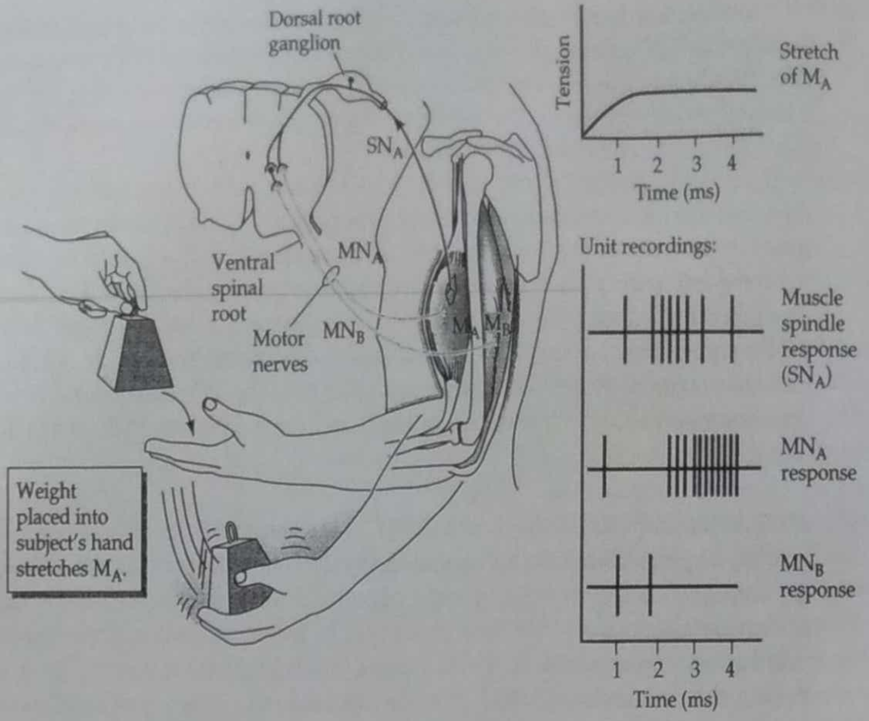
Muscle spindles respond primarily to stretch; the other receptors that respond to muscle tension—Golgi tendon organs—are especially sensitive to muscle contraction, or shortening. **Golgi tendon organs** are relatively insensitive to passive muscle stretch because they are associated with an elastic component (see Figure 11.9*a*, *b*, and *d*). Instead, they detect overloads that threaten to tear muscles and tendons. Stimulation of these receptors inhibits the motoneurons supplying the muscles that pull on the tendon and thus, by relaxing the tension, prevents mechanical damage.

Classic studies in physiology emphasized the importance of muscle spindles and Golgi tendon organs for movement. Mott (1895) and Sherrington (1898) showed that, after they cut the afferent fibers from muscles in monkeys, the monkeys failed to use the deafferented limb, even if the efferent connections from motoneurons to muscles were preserved. The deafferented limb is not paralyzed, since it can be activated (the motoneurons still innervate the muscles), but lack of information from the muscle leads to relative disuse. The arm dangles, apparently useless. But if the good arm is restrained (by a ball placed around the hand) the animal soon learns to use the deafferented arm and can become quite dexterous (Taub, 1976). Monkeys manage to do this the way Ian does, guiding their movements by using vision for feedback about how the arm is moving.

gamma motoneuron Also called *gamma efferent*. A motor neuron that innervates the contractile tissue in a muscle spindle.

alpha motoneuron A motoneuron that controls the main contractile fibers (extrafusal fibers) of a muscle.

Golgi tendon organ One of the receptors located in tendons that send impulses to the central nervous system when a muscle contracts.



11.10 The Stretch Reflex Circuit MN$_A$ is the motor nerve to muscle A (M$_A$); MN$_B$ is the motor nerve to muscle B (M$_B$), an antagonist to M$_A$. SN$_A$ is the sensory nerve from the muscle spindle of M$_A$. Characteristic responses at different stages in the circuit are shown at right.

Probably we all use channels of visual information to guide the motor system without being aware of it. Remember the young woman D.F. from Chapter 10? She could not report whether a slot was vertical or horizontal, yet when she was asked to insert a disk in the slot, she consistently rotated her hand to put it in smoothly. This finding suggests that even neurologically intact people unknowingly use visual cues to guide their movements (Goodale and Haffenden, 1998).

Movements Are Controlled at Several Nervous System Levels

The firing patterns of motoneurons are what determine the onset, coordination, and termination of muscle activity, but to really understand the physiology of movement, we need to know the source of the inputs to motoneurons. How do descending projections from the brain and spinal cord organize the activity of this final common pathway?

Spinal reflexes mediate "automatic" responses

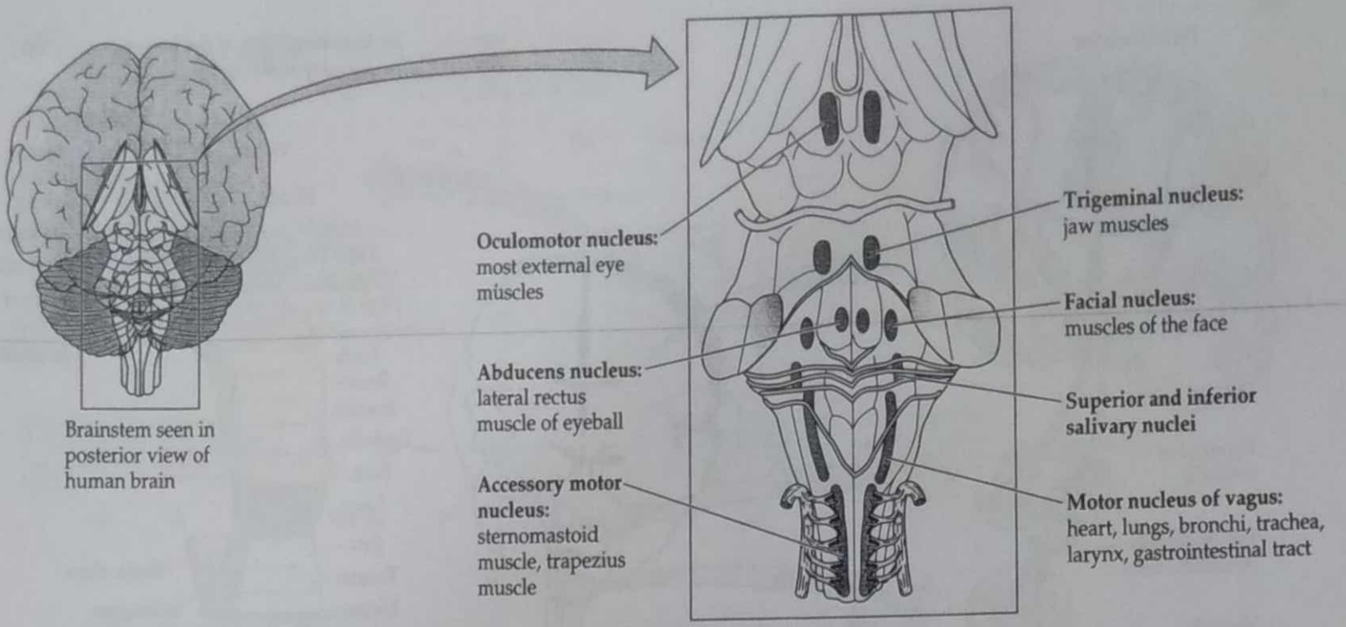
One way to study spinal mechanisms is to sever the connections between the brain and the spinal cord, producing a spinal animal, and then observe the forms of behavior that can be elicited below the level of the cut. (All voluntary movements that depend on brain mechanisms are lost, of course, as is sensation from the regions below the cut.)

A good example of automatic control at the spinal level is the **stretch reflex**—the contraction that results when a muscle stretches. In **Figure 11.10**, a weight added to the hand imposes sudden stretch on muscle A (M$_A$). The circuit that keeps us from dropping the load is one that links muscle spindles and the relevant muscles:

1. A disturbance is imposed.
2. The muscle is stretched.
3. Afferents from the muscle spindle are excited.
4. The spindle afferents connect directly—that is, monosynaptically—to the motoneurons that control the stretched muscle, exciting them.
5. The motoneurons stimulate the muscle to oppose muscle stretch.

This sequence describes a simple negative feedback system that tends to restore the limb to its "desired" position. Muscle spindle afferents also inhibit the motoneurons

stretch reflex The contraction of a muscle in response to stretch of that muscle.


Brainstem seen in posterior view of human brain
Oculomotor nucleus: most external eye muscles
Abducens nucleus: lateral rectus muscle of eyeball
Accessory motor nucleus: sternomastoid muscle, trapezius muscle
Trigeminal nucleus: jaw muscles
Facial nucleus: muscles of the face
Superior and inferior salivary nuclei
Motor nucleus of vagus: heart, lungs, bronchi, trachea, larynx, gastrointestinal tract

11.11 Motor Nuclei in the Brainstem Shown here from the rear, motor nuclei in the brainstem control muscles of the head and neck. The cranial nerves corresponding to these muscles are shown in Figure 2.9.

that supply the antagonistic muscle (M_B in Figure 11.10). Two synapses are required to inhibit the antagonistic motoneuron. Thus, in the situation illustrated in Figure 11.10, spindle information terminates on an interneuron, which inhibits the motoneuron that supplies M_B. The relaxation of antagonistic muscles ensures that they do not become injured by the sudden movement. A familiar example of the stretch reflex is the knee jerk used in medical examinations (see Figure 3.14). (Recall from Chapter 5 that the knee jerk reflex was abnormally slow in Chuck, who suffered from hypothyroidism.) Spinal reflexes are integrated and modulated by activity of the brain, which we consider next.

Pathways from the brain control different aspects of movements

Some muscles are controlled directly by the brain. The cranial motor nuclei of the brainstem send their axons to innervate muscles of the head and neck (**Figure 11.11**; see also Figure 2.9). But for all the other muscles, the brain has to send commands to the spinal cord and then the spinal cord controls the muscles. The brain sends these commands to the spinal cord through two major pathways: the pyramidal system (which we discuss next) and extrapyramidal motor system (described later in this chapter).

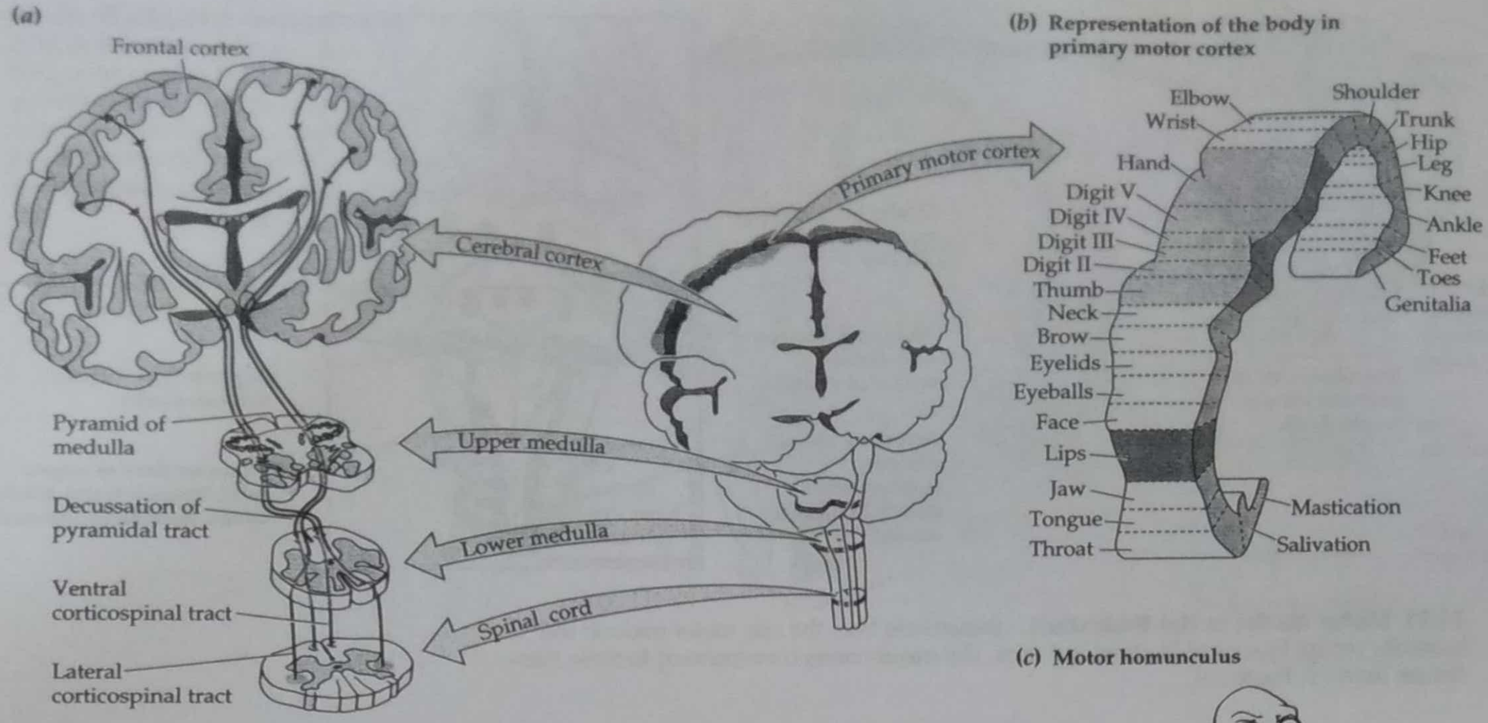
The **pyramidal system** (or **corticospinal system**) consists of neuronal cell bodies within the cerebral cortex and their axons, which pass through the brainstem, forming the pyramidal tract to the spinal cord (**Figure 11.12*a***). The pyramidal tract is seen the most clearly where it passes through the floor of the medulla. In a cross section of the medulla, the tract is a wedge-shaped anterior protuberance (pyramid) on each side of the midline. In the medulla the pyramidal tract from the right hemisphere crosses the midline to innervate the left spinal cord, and vice versa.

Because the pyramidal tract crosses the midline (technically known as a *decussation*) in the medulla, the right tract controls the left side of the body while the left tract controls the right. Lesions of the pyramidal system deprive the patient of the ability to move individual joints and limbs.

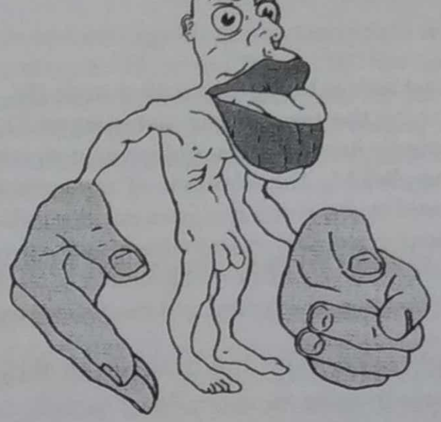
Many of the axons of the pyramidal tract originate from neurons in the **primary motor cortex** (**M1**), or precentral gyrus, just anterior to the central sulcus (**Figure 11.12*b***). Many of these cells are large neurons (called *Betz cells*) in layer V of the primary motor cortex.

pyramidal system or corticospinal system The motor system that includes neurons within the cerebral cortex and their axons, which form the pyramidal tract.

primary motor cortex (M1) The apparent executive region for the initiation of movement; primarily the precentral gyrus.


(a)
Frontal cortex
Primary motor cortex
Cerebral cortex
Upper medulla
Lower medulla
Spinal cord
Pyramid of medulla
Decussation of pyramidal tract
Ventral corticospinal tract
Lateral corticospinal tract
(b) Representation of the body in primary motor cortex
Elbow
Wrist
Hand
Digit V
Digit IV
Digit III
Digit II
Thumb
Neck
Brow
Eyelids
Eyeballs
Face
Lips
Jaw
Tongue
Throat
Shoulder
Trunk
Hip
Leg
Knee
Ankle
Feet
Toes
Genitalia
Mastication
Salivation

(c) Motor homunculus



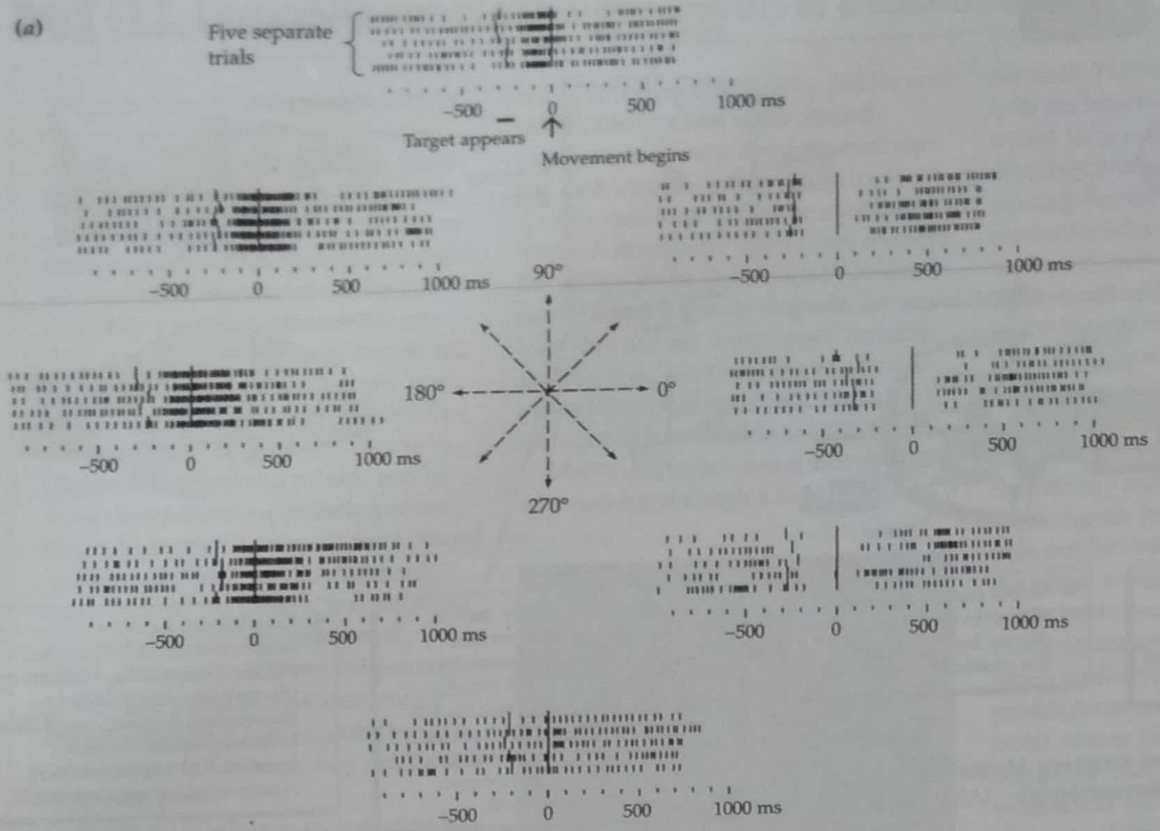
11.12 The Pyramidal System and Primary Motor Cortex (a) In the pyramidal (or corticospinal) motor system, most of the fibers cross to the opposite side in the medulla (at the decussation of the pyramidal tract) and descend the spinal cord in the lateral corticospinal tract. (*b*) The primary motor cortex (M1) is a strip just in front of the central sulcus. Regions controlling motor responses of different parts of the body are shown here in relative sequence and size. (*c*) The proportions of this homunculus show the relative sizes of primary-motor-cortex representations of parts of the body.

Primary motor cortex is an executive motor control mechanism—and more

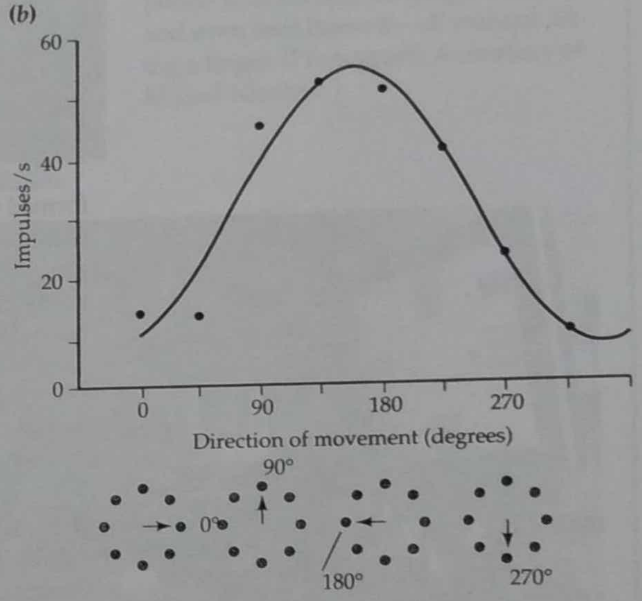
In humans, brain damage to the primary motor cortex (M1) produces partial paralysis on the side of the body opposite the brain lesion (i.e., the *contralateral* side of the body). The disturbance is greatest in distal muscles, such as those of the hand. Humans with these lesions are generally disinclined to use the affected limb.

Early-twentieth-century researchers like Wilder Penfield, whom we discussed at the start of Chapter 2, used electrical stimulation to develop functional maps of human primary motor cortex. Disproportionately large regions in the maps of M1 are devoted to the body parts involved in the most elaborate and complex movements. For example, humans and other primates have extremely large cortical fields concerned with hand movements (see Figure 11.12*b* and *c*).

In primates the pyramidal tract has some monosynaptic connections with spinal motoneurons, but most pyramidal-tract neurons influence spinal motoneurons through polysynaptic routes and share control of these motor cells with other descending influences.

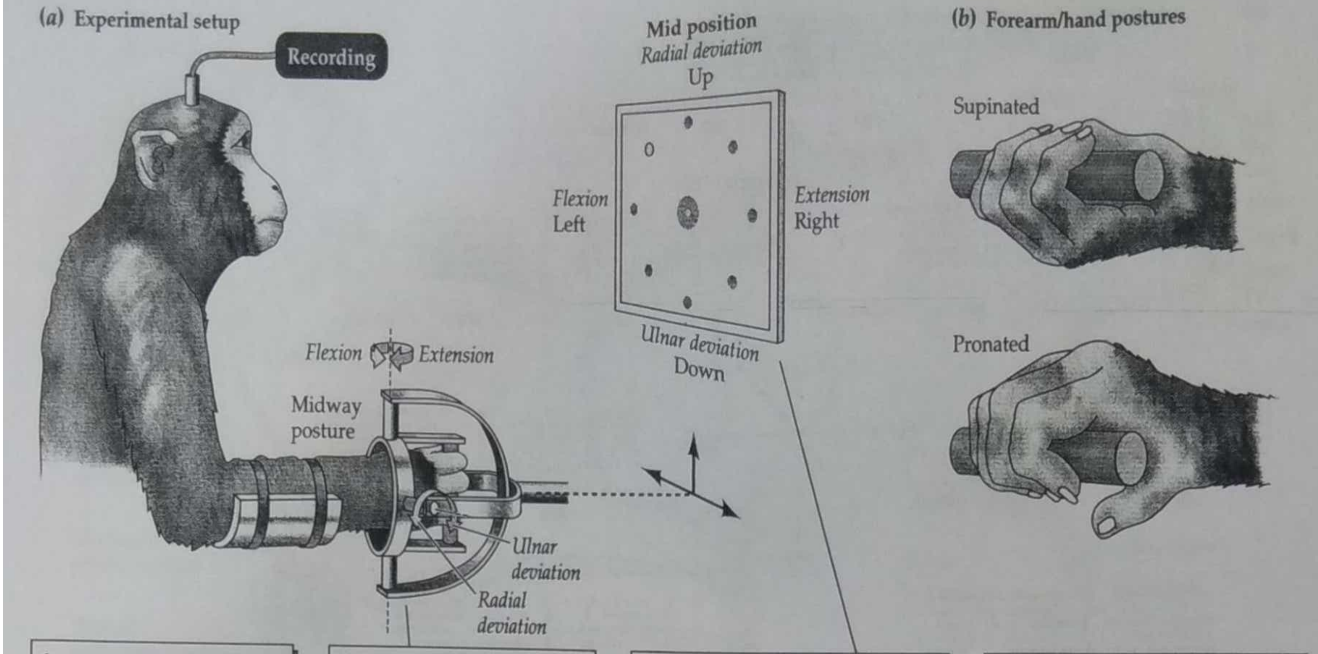


11.13 Directional Tuning of Motor Cortex Cells (*a*) Shown here is the activity of a single neuron during arm movement toward a target in eight different directions. Each horizontal record in the eight blocks of data represents one of five trials. Note that this cell consistently fires before the arm moves in the direction from 90° to 180° to 270°, and it is silent before movements in the other directions. (*b*) The average frequency of discharge during the interval before movement changed depending on the direction. (From Georgopoulos et al., 1982.)



By recording from M1 neurons of monkeys that were trained to make free arm movements in eight possible target directions (Georgopoulos et al., 1993), we can eavesdrop on the commands originating there (**Figure 11.13*a***). Many M1 cells change their firing rates according to the direction of the movement, but for any one cell, discharge rates are highest in one particular direction (**Figure 11.13*b***). Therefore, each cell carries only partial information about the direction of reaching. When we average the activity of several hundred M1 neurons at once, we can predict fairly well which direction the animal will reach with its arm. Given the millions of neurons in this region, a larger sampling would presumably provide an even more accurate prediction.

A long-standing controversy has raged over whether *muscles* or *movements* are represented in M1. That is, does activity of a cortical motor neuron encode a relatively simple parameter such as contraction of a particular muscle, or a more abstract parameter such as a particular movement of the hand through space? To address this controversy, experimenters trained a monkey to perform rapid tracking movements using the hand and wrist (Kakei et al., 1999). As **Figure 11.14** shows, the animal grasped a handle that could be rotated along the two axes of wrist motion. Movement of the handle controlled


(*a*) Experimental setup

(*b*) Forearm/hand postures

1. At start of session, head is fixed in position and electrodes are placed for recording from individual motor cortex neurons.
2. Before trial, forearm is placed in the position shown here or in one of the positions shown in *b*.
3. To start trial, monkey moves cursor (blue dot) to central target; 0.75 to 1.5 seconds later, one of the peripheral targets appears (yellow). When central target is extinguished 3 seconds later, monkey must move the cursor rapidly to peripheral target to obtain reward.
4. **Conclusion:** Activity of one-third of M1 neurons corresponded to muscle movements, but activity of one-half corresponded to movements in space, regardless of hand posture. So, both muscles and movements are represented by neurons in M1.

11.14 Do Neurons in the Primary Motor Cortex Represent Muscles or Movements? (After Kakei et al., 1999.)

the position of a cursor on a computer screen. After much training (over 8 years!), the monkey performed well.

The experimenters then recorded the activity of single cells in M1 as the monkey performed from different starting positions. A substantial group of M1 neurons (32%) displayed changes in activity that corresponded to *muscle* contractions, but an even larger group of neurons (50%) showed activity that corresponded to *movement* in space, regardless of hand posture. In other words, these cells were active whenever the monkey moved its hand in a particular direction, no matter which muscles were needed to accomplish that movement. Thus, *both* movements and, to a lesser extent, muscles are represented in M1. In theory, if we can record the activity of motor cortex to predict what movement the person is calling for, we might be able to use that information to guide a robotic arm—the subject of **Box 11.1**.

THE ROLE OF PRIMARY MOTOR CORTEX IN LEARNING Several studies with both experimental animals and humans demonstrated that motor representations in M1 change as a result of training. Maps prepared from electrical stimulation in M1 show changes as an animal learns new skills—for example, a visually guided tracking movement with the arm (J. N. Sanes and Donoghue, 2000) or a precision grasping task (Nudo et al., 1996).

In humans, the width of the precentral gyrus as seen with MRI offers an estimate of the size of M1. The gyrus is significantly wider in piano players, especially in the hand representation area (see Figure 11.12*b* and *c*), than in nonmusician control subjects. The younger the musician was at the start of musical training, the larger the gyrus is in adulthood (Amunts et al., 1997), so this expansion of M1 seems to be in response to the experience of musical training.

Transcranial magnetic stimulation (*TMS*) uses a brief magnetic field to stimulate cortical neurons beneath the skin and skull (see Chapter 2). In one study (Classen et al.,

BOX 11.1 Cortical Neurons Control Movements of a Robotic Arm

Signals from rat motor cortex can be used to control one-dimensional movements of a robotic arm, paralleling the movement of the rat's own arm (Chapin et al., 1999). If the rats receive visual feedback and are rewarded for successful movements of the robotic arm, they progressively cease to produce overt arm movements and let the robotic arm accomplish the task. Investigators have also used microwires implanted in the cortex of owl monkeys (Figure A) to control a robotic arm in three dimensions, reproducing movements to reach for pieces of food placed in different positions, pick them up, carry them to the mouth, and return to the start position (Wessberg et al., 2000). The results of these studies suggested that paralyzed patients might learn to operate a robotic arm by cortical activity even though they can't move their own limbs.

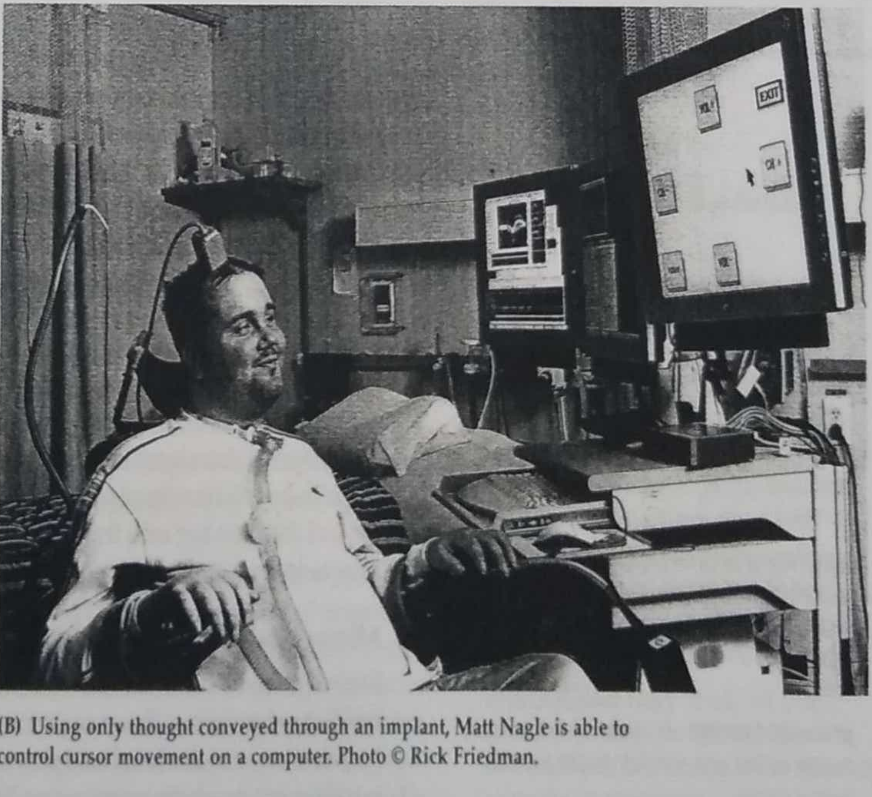
Matthew Nagle was an innocent bystander when a brawl broke out on the beach one night, but it was he who was stabbed in the neck and left paralyzed below the shoulders. A former football player, Matt was determined to regain control of his life. He had a surgical team implant 96 microwires into his primary motor cortex to record the activity of neurons there. The firing pattern of the neurons was recorded by a computer. As Matt imagined moving his arm to hit various targets on the screen, the computer eavesdropped on the neuronal firing and a program tried to figure out which firing pattern corresponded to movement in each direction. After this "calibration," the program used the firing pattern to move the cursor in the direction that Matt was imagining his arm was moving.

With just 4 days of training, Matt learned to move the cursor on the computer so that he could open e-mail and play a simple video game (Figure B). When the computer was interfaced with a prosthetic limb, Matt was able to flex the prosthetic hand and make rudimentary actions with a jointed robotic arm (Hochberg et al., 2006). But he was never able to make really smooth movements of even the computer cursor, and each day's calibration took about a half hour before he could even begin. Furthermore, after a few months the ability of the electrodes to detect neural firing began to degrade, for reasons that are not understood. So after about a year, Matt had the implant removed, but he is optimistic that a better system will be available soon.

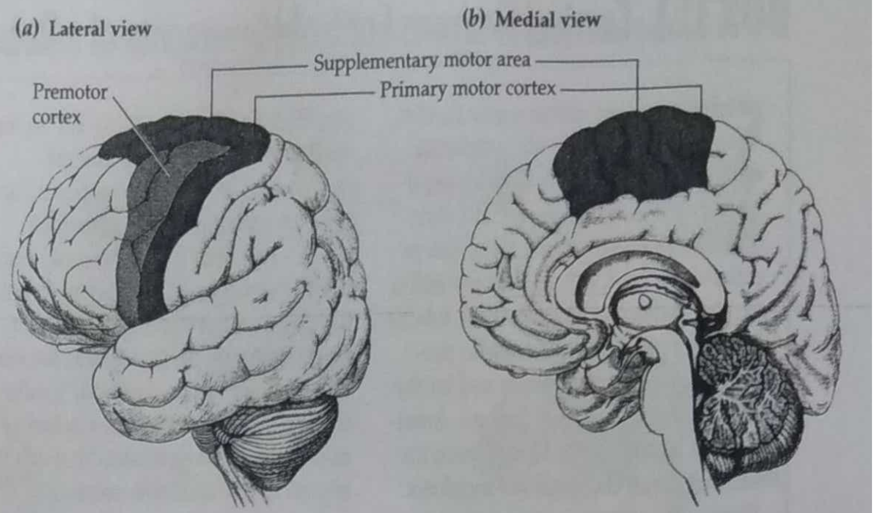
Matt's implants were connected by a wire passing through a hole drilled in his skull. That opening had to be carefully maintained to avoid infection, but it may be possible to make an implant that uses radio waves, rather than wires passing through the skull, to tell the computer which neurons are firing. Animal work indicates that recording more neurons should give an even better idea of the direction that Matt intended for his arm to move.

Another possibility is to implant the electrodes in premotor cortex, with the idea that these are the neurons that call on primary motor cortex, so the neuronal signals for the intent to move the arm can be detected sooner. Again, the neuronal activity would be detected by a computer and used to move the computer cursor or a robotic limb. Monkeys given such an implant became very proficient at moving a cursor on a computer screen (Santhanam et al., 2006). Someday Matt may be able to direct his wheelchair about town, chat on the phone with friends, exchange e-mails, and even feed himself—all without lifting a finger. (Photograph A courtesy of Miguel Nicolelis.)

(A) Owl monkey perched atop a robotic arm.



(B) Using only thought conveyed through an implant, Matt Nagle is able to control cursor movement on a computer. Photo © Rick Friedman.



11.15 Human Motor Cortical Areas (a) The primary motor cortex (M1) lies just anterior to the central sulcus. Anterior to the primary motor cortex are the premotor cortex and the supplementary motor area (SMA), which together make up the nonprimary motor cortex. (b) The SMA lies mainly on the medial surface of the cerebral hemispheres.

1998), focal TMS was used in human volunteers to evoke isolated thumb movements in a particular direction. Then the subjects practiced moving the thumb in a different direction for 15 to 30 minutes. The same TMS was then found to evoke thumb movement in the *new* direction for several minutes before the response reverted to the original direction. (This rapid change seems similar to the retuning of auditory cortical receptors during stimulation at another frequency, as noted in Chapter 9.)

Nonprimary motor cortex aids motor sequencing

Just anterior to M1 are cortical regions that are also important for motor control. Because they are not primary motor cortex, they are called *nonprimary motor cortex*. **Nonprimary motor cortex** consists of two main regions: the **supplementary motor area (SMA)**, which lies mainly on the medial aspect of the hemisphere, and the **premotor cortex**, which is anterior to the primary motor cortex (**Figure 11.15**). Patients with lesions of the premotor cortex retain fine motor control of the fingers but are impaired in their stance and gait, and in the coordination of the two hands. In contrast, patients with bilateral damage to the SMA are unable to move voluntarily (only some automatic and reflex movements remain), suggesting that this region initiates movement sequences (Tanji, 2001).

Studies of localized cerebral blood flow and metabolism reveal that, in simple tasks, such as keeping a spring compressed between two fingers of one hand, blood flow increases markedly in the hand area of the opposite M1 (P. E. Roland, 1980, 1984). Increasing the complexity of motor tasks to a sequence of behaviors extends the area of increased blood flow to the SMA, supporting the idea that *sequences* of movement are encoded here. When subjects mentally *rehearse* the complex movement sequence without actually doing it, the enhanced blood flow is seen only in the SMA, not in M1. In contrast, the premotor cortex is activated when motor sequences are guided externally by stimuli (Halsband et al., 1994; Larsson et al., 1996) rather than generated internally.

A subset of premotor neurons is also activated when objects are brought close to a monkey's face or hand. If the lights are then turned out, some of these neurons continue to fire even if the object is silently moved, suggesting that the cells are coding for where the monkey thinks the object is (Graziano et al., 1997). When the lights are turned back on and the monkey sees that the object is gone, the neurons cease firing. Such neurons may help us reach out for objects that are no longer visible.

Mirror neurons in premotor cortex track movements in others

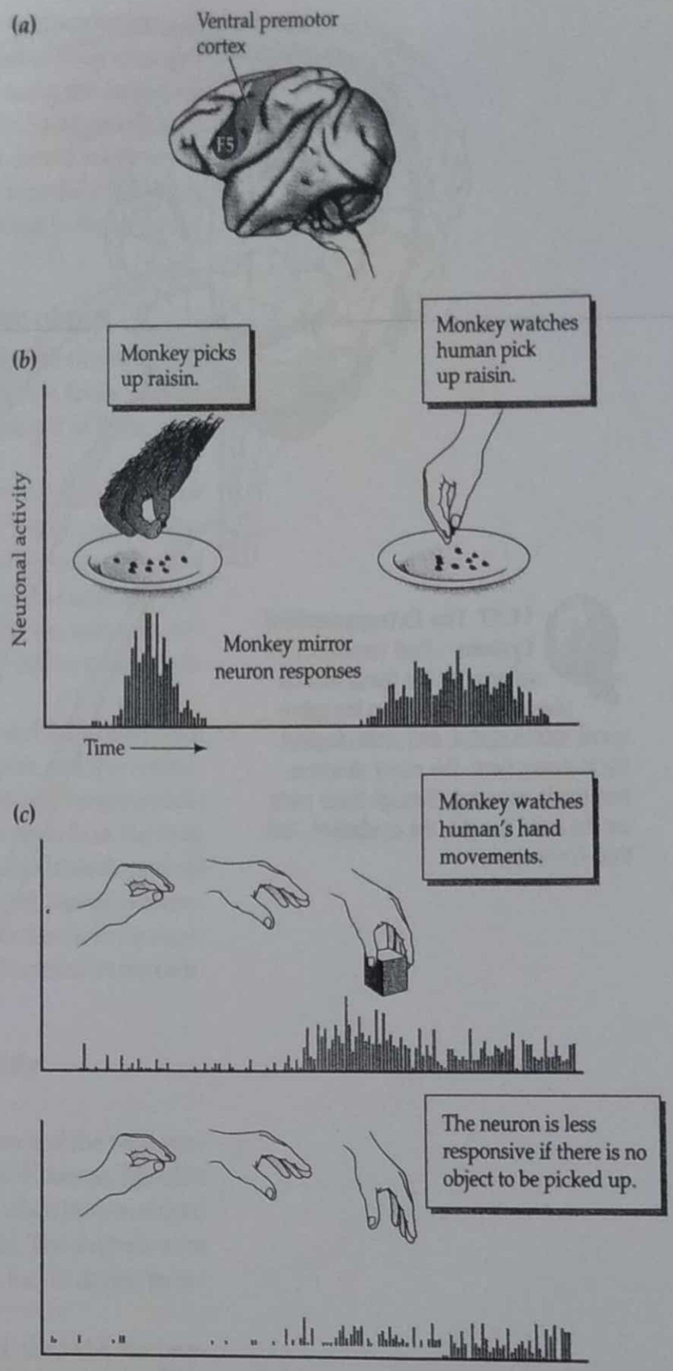
Premotor cortex also contains another population of remarkable neurons that seem to fulfill two functions. These neurons fire shortly before a monkey makes a very particular movement of the hand and arm to reach for an object; different neurons seem to trigger different reaching movements. These results suggest that these neurons trigger spe-

nonprimary motor cortex Frontal lobe regions adjacent to the primary motor cortex that contribute to motor control and modulate the activity of the primary motor cortex.

supplementary motor area (SMA) A region of nonprimary motor cortex that receives input from the basal ganglia and modulates the activity of the primary motor cortex.

premotor cortex A region of nonprimary motor cortex just anterior to the primary motor cortex.

11.16 Mirror Neurons (a) In the ventral portion of premotor cortex, known as *area F5*, many mirror neurons are found. (b) These neurons fire just before a monkey reaches for an object, such as a raisin (*left*), or when the monkey sees a human experimenter reach for a raisin in the same manner (*right*). (c) This mirror neuron fired when the monkey reached for a box or, as here, it observed a human reaching for a box (*top*). The mirror neuron also fires, but much less vigorously, if there is no box for the human to grasp (*bottom*) (Umilta et al., 2001). (After Rizzolatti et al., 2006.)


(a)
Ventral premotor cortex
F5
(b)
Monkey picks up raisin.
Monkey watches human pick up raisin.
Neuronal activity
Monkey mirror neuron responses
Time →
(c)
Monkey watches human's hand movements.
The neuron is less responsive if there is no object to be picked up.

cific movements. But these neurons also fire whenever the monkey sees *another* monkey (or a human) make that same movement. These cells are called **mirror neurons** because they fire as though the monkey were imitating the movements of the other individual (**Figure 11.16**). They are matching the observed behavior with an internal motor representation of that behavior, as if the observer were imagining doing the same thing as the observed monkey.

MRI and EEG studies indicate that mirror neurons are also found in adult humans (Buccino et al., 2004) and children (J. F. Lepage and Theoret, 2006). In the classic "mirror game," in which one person moves slowly and the other tries to imitate the first person as closely as possible, these neurons are probably at work. They have also been seen in other areas of frontal (Nelissen et al., 2005) and parietal cortex (Fogassi et al., 2005). The activity of these neurons suggests that they are important in the understanding of other individuals' actions and in attempts to imitate those actions (Rizzolatti and Craighero, 2004).

It is intriguing to think that mirror neurons may help us understand what other people are doing, because the idea suggests a neural basis for empathy. Thus there has been a great deal of speculation about the function of mirror neurons in the imitating behavior of human infants, the evolution of language, and other behavior. Some have speculated that people with autism, which is characterized by a failure to anticipate other people's thinking and action, may have a deficit in mirror neuron activity (J. H. Williams et al., 2006).

Extrapyramidal Systems Also Modulate Motor Commands

In addition to the corticospinal outflow through the pyramidal tract, many other motor tracts run from the forebrain to the brainstem and spinal cord. Because these tracts are outside of the pyramids of the medulla, they and their connections are called the **extrapyramidal system** (**Figure 11.17**). In general, lesions of the extrapyramidal system do not prevent the movement of individual joints and limbs, but they do interfere with spinal reflexes, usually exaggerating them.

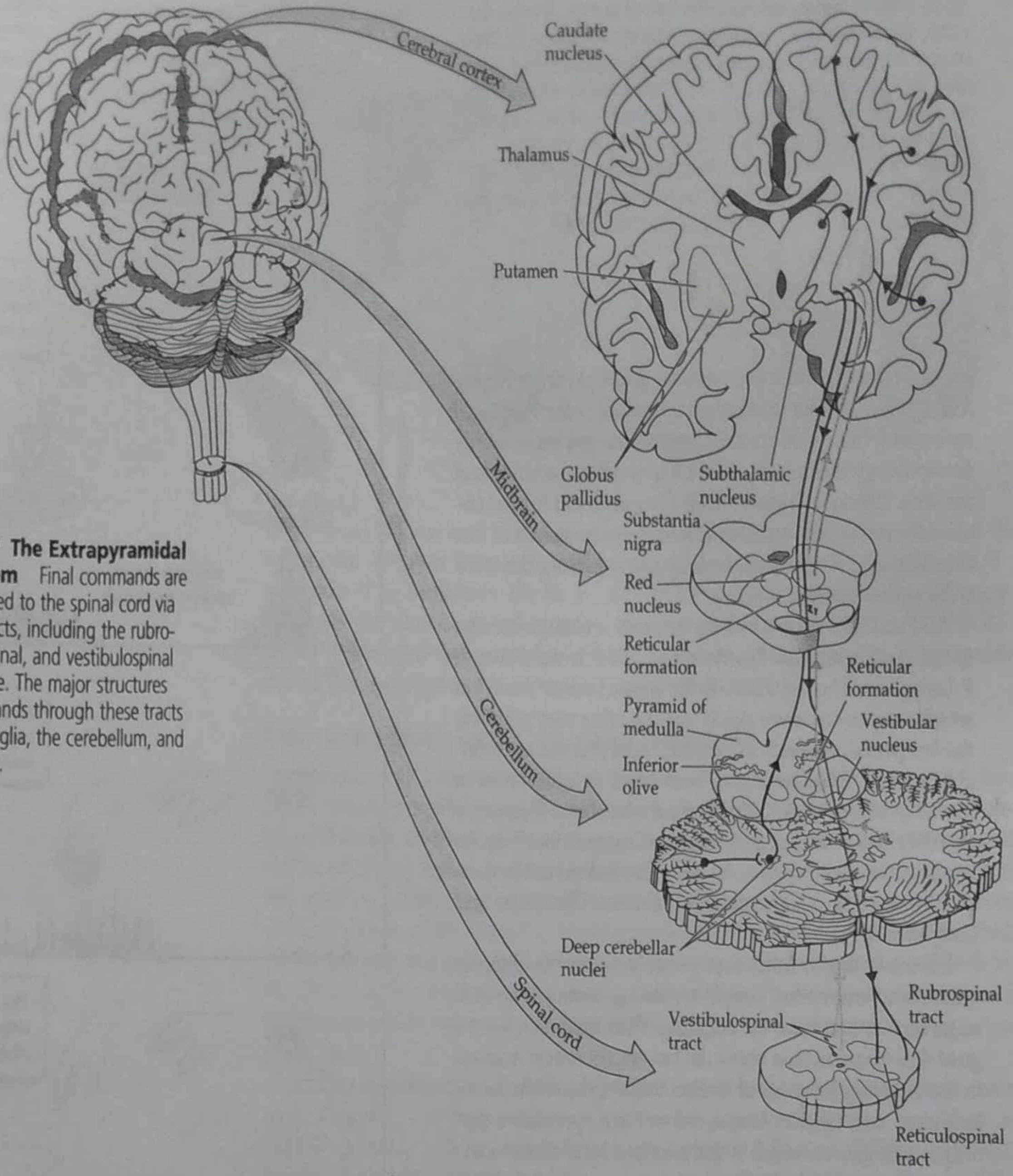
The extrapyramidal system communicates to the spinal cord through two principal pathways: the reticulospinal and rubrospinal tracts. The extensive pool of interconnected neurons called the **reticular formation** modulates various aspects of movements. Some zones of the reticular formation facilitate movements; other zones are inhibitory. These effects are transmitted in descending tracts known as **reticulospinal tracts** that arise from the reticular formation and connect to spinal interneurons, where they influence spinal motor circuitry. The second extrapyramidal outflow originates from the

mirror neuron A neuron that is active when an individual makes a particular movement, but is also active when an individual sees another individual make that same movement.

extrapyramidal system A motor system that includes the basal ganglia and some closely related brainstem structures.

reticular formation An extensive region of the brainstem (extending from the medulla through the thalamus) that is involved in arousal.

reticulospinal tract A tract of axons arising from the brainstem reticular formation and descending to the spinal cord to modulate movement.


Cerebral cortex
Caudate nucleus
Thalamus
Putamen
Globus pallidus
Subthalamic nucleus
Midbrain
Substantia nigra
Red nucleus
Reticular formation
Pyramid of medulla
Inferior olive
Reticular formation
Vestibular nucleus
Cerebellum
Deep cerebellar nuclei
Spinal cord
Vestibulospinal tract
Rubrospinal tract
Reticulospinal tract

11.17 The Extrapyramidal System Final commands are delivered to the spinal cord via several tracts, including the rubrospinal, reticulospinal, and vestibulospinal tracts shown here. The major structures that send commands through these tracts are the basal ganglia, the cerebellum, and their connections.

midbrain's **red nucleus** and so is called the **rubrospinal tract** (the Latin *ruber* means "red"), terminating in the spinal cord to regulate motor output.

The basal ganglia modulate movements

The **basal ganglia** include a group of interconnected forebrain nuclei: the caudate nucleus, putamen, and globus pallidus. Closely associated with these structures are two nuclei in the midbrain: the substantia nigra and the subthalamic nucleus. Figure 11.17 shows the locations of these structures. The caudate nucleus and putamen together are referred to as the **striatum**.

Each of these structures receives input from wide areas of the cerebral cortex and sends much of its output back to the cortex via the thalamus, forming a loop from the cortex through the basal ganglia and thalamus and back to the cortex. Lesions of basal ganglia in humans produce movement impairments that seem quite different from those that follow interruption of the pyramidal system. Two disorders described later in the chapter—Parkinson's disease and Huntington's disease—are caused by degeneration of the basal ganglia.

red nucleus A brainstem structure related to motor control.

rubrospinal tract Axons arising from the red nucleus in the midbrain and innervating neurons of the spinal cord.

basal ganglia A group of forebrain nuclei (caudate nucleus, globus pallidus, and putamen) found deep within the cerebral hemispheres.

striatum The caudate nucleus and putamen together.

Lesions and recordings of single neurons during motor responses indicate that each structure of the basal ganglia contains a topographic representation of body musculature (DeLong et al., 1984). The basal ganglia play a role in determining the amplitude and direction of movement rather than the initiation of actions. The basal ganglia thus seem to modulate the activity initiated by other brain circuits that control movements, such as the cortical system (see Figure 11.4). The basal ganglia are especially important in the performance of movements influenced by memories, in contrast to those guided by sensory control (Graybiel et al., 1994).

The cerebellum affects programs, timing, and coordination of acts

Across vertebrate groups, the size of the cerebellum varies according to the range and complexity of movements. For example, the cerebellum is much larger in fishes with extensive locomotor behavior than it is in less-active fishes; it is also larger in flying birds than in bird species that do not fly.

Recall from Chapter 2 that the outer layers of the cerebellum are called the *cerebellar cortex* and are dominated by a sheet of large multipolar cells called *Purkinje cells* (see Figure 2.16). All output of the cerebellar cortex travels via the axons of Purkinje cells, all of which synapse with the deep cerebellar nuclei. At these synapses, Purkinje cells produce only inhibitory postsynaptic potentials. Hence all the circuitry of the extensive cortical portion of the cerebellum, which also includes 10 billion to 20 billion granule cells in humans, guides movement by *inhibiting* neurons.

Inputs to the cerebellar cortex come both from sensory sources and from other brain motor systems. Sensory inputs include the muscle and joint receptors, and the vestibular, somatosensory, visual, and auditory systems. Both pyramidal and nonpyramidal pathways contribute inputs to the cerebellum and in turn receive outputs from the deep nuclei of the cerebellum. It has been suggested that the cerebellum elaborates neural "programs" for the control of skilled movements, particularly rapid, repeated movements that become automatic. This role of the cerebellum in learned motor responses is discussed in Chapter 18. Synaptic plasticity in the cerebellum is described on the website in **A Step Further: Cerebellar Synaptic Depression**.

The cerebellum and the basal ganglia contribute differently to the modulation of motor functions

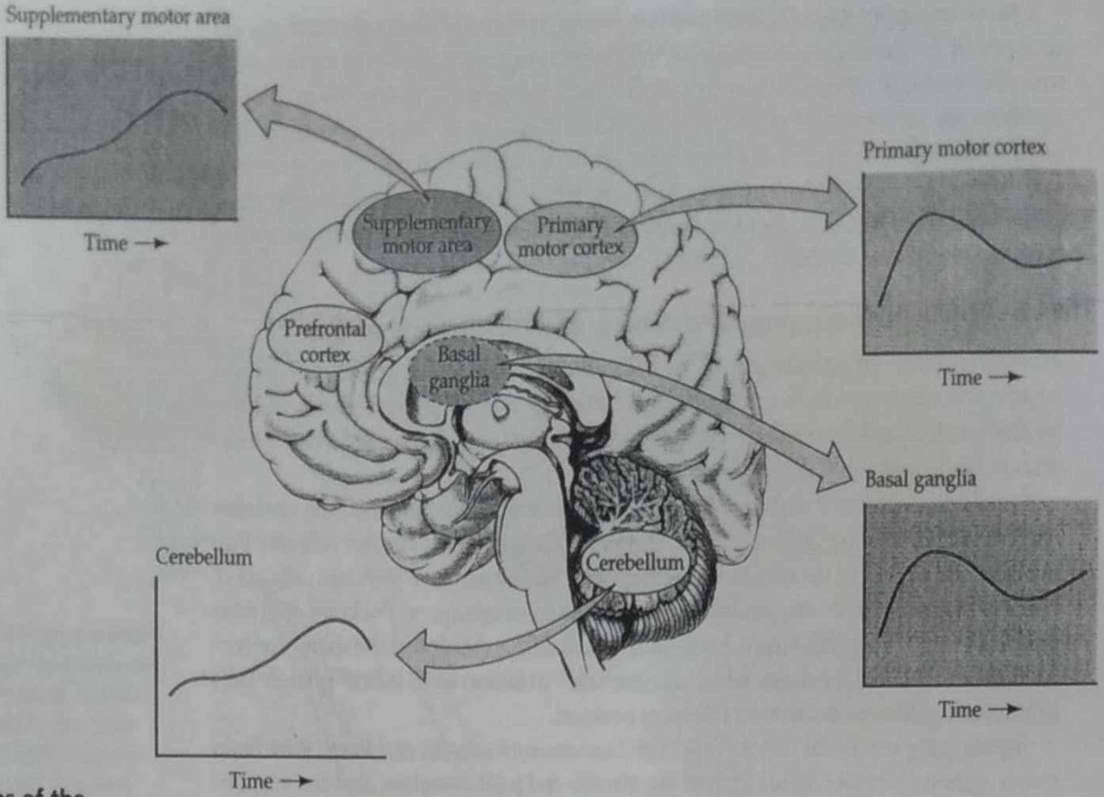
The foregoing discussion and Figure 11.4 indicate that the cerebellum and the basal ganglia occupy rather similar positions in modulating motor functions. However, Yijun Liu et al. (1999) found differences in the activity of these brain regions when they examined fMRI responses of subjects performing a tactile discrimination task. The subjects were given two similarly shaped objects—one in each hand—and they had to decide by active touching whether the objects were the same or different.

Changing patterns of activity during this task were found in M1, the SMA, the cerebellum, and the basal ganglia. Cerebellar activity correlated significantly with activity of the SMA but not M1, whereas basal ganglia activity correlated more strongly with activity of M1 than of the SMA. Thus, although the task appears to require the activity of five brain regions (**Figure 11.18**), the cerebellum and basal ganglia show temporally and anatomically different contributions.

The cerebellum and basal ganglia also contribute differently to the task of reaching. As we saw in Figure 11.1*b*, patients with Huntington's disease, who suffer from damage to the basal ganglia, show impairment especially toward the end of a reach, when corrections are made. In contrast, patients with cerebellar damage show errors especially in the initial direction of reach (M. A. Smith et al., 2000).

Endogenous oscillators drive many repetitive movements

However it is accomplished, most locomotion is rhythmic. For all animals, moving about consists of repetitive cycles of the same act, whether the beating of wings or the repetitive swinging of legs. Many rhythmic movements are generated by mechanisms within the spinal cord. These endogenous rhythms are normally modulated by feedback, but



11.18 Contributions of the Cerebellum and Basal Ganglia to the Modulation of Movements Cerebellar activity correlates with that of the supplementary motor area; basal ganglia activity correlates with that of primary motor cortex. (After Yijun Liu et al., 1999.)

they can function independently of brain influences or afferents. The term **central pattern generator** is used to refer to the neural circuitry responsible for generating rhythmic patterns of behavior as seen in walking. Electromyographic records of hindlimb muscles of cats with spinal cord section and dorsal root cuts reveal a "walking" pattern that lasts for seconds when a single dorsal root is briefly stimulated electrically (P. Grillner et al., 1991; S. Grillner, 1985). Thus the brain does not generate the essential rhythm in the spinal cord, but normally controls the onset of the rhythm and provides corrections as needed.

Disorders of Muscle, Spinal Cord, or Brain Can Disrupt Movement

Disorders at any level in the motor system—muscles, neuromuscular junctions, spinal cord, or brain regions—can impair movement. In the discussion that follows we will consider examples at each of these levels.

In muscular dystrophy, biochemical abnormalities cause muscles to waste away

Several muscle diseases are characterized by biochemical abnormalities that lead to structural changes in muscle; these disorders are referred to as **muscular dystrophy** (from the Greek *dys*, "bad," and *trophe*, "nourishment"). As the name implies, in various muscular dystrophies the muscles waste away (Blake et al., 2002).

Duchenne's muscular dystrophy strikes almost exclusively boys, beginning at the age of about 4 to 6 years and leading to death within a decade. Pedigrees show that the disorder is a simple Mendelian trait—caused by a single gene, in this case carried on the X chromosome. When the gene was identified, it was named *dystrophin*. In some ways the name is unfortunate because the dystrophin protein, when normal, does *not* lead to dystrophy. **Dystrophin** is normally produced in muscle cells and may play a role in regulating internal calcium stores. Because females have two X chromosomes, even if one carries the defective copy of the dystrophin gene, the other X chromosome can still produce normal dystrophin. But about half the sons of such females will receive the defective

central pattern generator Neural circuitry that is responsible for generating a rhythmic pattern of behavior, such as walking.

muscular dystrophy A disease that leads to degeneration of and functional changes in muscles.

dystrophin A protein that is needed for normal muscle function.

gene and, because they have only the one X chromosome, will be afflicted with the disease. In the hope of halting the loss of muscle fibers in Duchenne's, efforts are under way to induce the muscles of boys with this disease to express normal dystrophin.

The immune system may impair motor function by attacking neuromuscular junctions

Several poisons affect neuromuscular junctions. For example, snake bites can cause neuromuscular blocks because the venom of some highly poisonous snakes contains substances (such as bungarotoxin) that block postsynaptic acetylcholine receptors. If the neuromuscular junctions to the muscles for breathing are blocked, the victim suffocates.

Studies of bungarotoxin led to an understanding of a debilitating neuromuscular disorder, **myasthenia gravis** (from the Greek *mys*, "muscle," and *asthenes*, "weak"; and the Latin *gravis*, "grave" or "serious"). This disorder is characterized by a profound weakness of skeletal muscles. The disease often first affects the muscles of the head, producing symptoms such as drooping of the eyelids, double vision, and slowing of speech. In later stages, paralysis of the muscles that control swallowing and respiration become life-threatening.

Myasthenia gravis is an **autoimmune disorder**: most cases result from the patient's developing antibodies that attack his own acetylcholine receptors, disrupting neuromuscular junctions. In other cases the antibodies are directed toward other proteins that are associated with the acetylcholine receptor. Treatment often consists of prescribing drugs to suppress the immune system (Richman and Agius, 2003).

Motoneuron pathology leads to motor impairments and death

Virus-induced destruction of motoneurons—for example, by the disease polio—was once a frightening prospect around the world. **Polioviruses** destroy motoneurons of the spinal cord and, in more severe types of the disease, cranial motoneurons of the brainstem. Because the muscles are no longer called on to contract, they atrophy. If the muscles controlling breathing are lost, the person must rely on a ventilator to stay alive.

In the late 1930s the sad end of the brilliant baseball career of New York Yankees star Lou Gehrig brought public awareness to an unusual degenerative disorder in which the motoneurons of the brainstem and spinal cord die and their target muscles waste away. This syndrome is formally known as **amyotrophic lateral sclerosis** (**ALS**), commonly called *Lou Gehrig's disease*. The origins of the disease remain a mystery, but a wide range of causal factors are under investigation, including premature aging, toxic minerals, viruses, immune responses, and endocrine dysfunction.

About 10% of ALS cases are hereditary. The pedigrees of several afflicted families indicate that this rare form of ALS is a single-gene disorder. The particular gene has been isolated (Andersen et al., 1995) and found to encode an enzyme: copper/zinc superoxide dismutase. When scientists produced transgenic mice that, in addition to their own normal copies of the enzyme, carried a copy of the defective human gene, these animals displayed an ALS-like syndrome (Gurney et al., 1994). Their muscles wasted away and their motoneurons died, leading to an early death. Studies of this mouse model of ALS suggest that motoneurons may die because their mitochondria are damaged (J. Liu et al., 2004).

Spinal cord injuries cause some motor impairments

Vehicular accidents, violence, falls, and sports injuries cause many human spinal injuries that result in motor impairment. Injuries to the human spinal cord commonly develop from force to the neck or back, breaking a bone that compresses the spinal cord. If the spinal cord is severed completely, immediate paralysis results, and reflexes below the level of injury are lost—a condition known as **flaccid paralysis**. Flaccid paralysis generally results only when a considerable stretch of the spinal cord has been destroyed. When the injury severs the spinal cord without causing widespread destruction of tissue, reflexes below the level of injury may become excessive because the intact tissue lacks the dampening influence of brain inhibitory pathways.

myasthenia gravis A disorder characterized by a profound weakness of skeletal muscles; caused by a loss of acetylcholine receptors.

autoimmune disorder A disorder caused when a person's immune system mistakenly attacks her or his own body, thereby interfering with normal functioning.

polioviruses A class of viruses that destroy motoneurons of the spinal cord and brainstem.

amyotrophic lateral sclerosis (ALS) Also called *Lou Gehrig's disease*. A disease in which motoneurons and their target muscles waste away.

flaccid paralysis A loss of reflexes below the level of transection of the spinal cord.

An estimated 250,000 to 400,000 individuals in the United States have spinal cord injuries. Actor Christopher Reeve (**Figure 11.19**) suffered such an injury while falling from a horse. He and his wife founded an organization (www.christopherreeve.org) to inform people about spinal cord injuries and mobilize research to repair such injuries. With diligent training and physical therapy, Reeve regained some sensation from his body and learned to move some of his fingers, which doctors regarded as quite unusual, but he died without ever achieving his dream of walking again.

The hope of reconnecting the injured spinal cord no longer seems far-fetched. Months after the spinal cord is severed in lampreys, the fish can swim again without any therapeutic intervention (A. H. Cohen et al., 1989), but they seem unique among vertebrates in this regard. Four main strategies for reconnecting the brain and spinal cord in humans are being investigated (**Figure 11.20**):

1. To provide stem cells that might differentiate into new neurons to send new axons across the break (Okano et al., 2003).
2. To transplant glial cells that promote regeneration in the CNS. Recall from Chapter 9 that olfactory receptor neurons can be continuously produced throughout life and send out new axons. When Ying Li et al. (1997) took specialized glial cells (called *ensheathing cells*) from the olfactory bulb and used them as a bridge across spinal cord cuts in rats, the corticospinal axons regenerated across the injury, and the animals eventually regained use of their forepaws. Efforts are under way to genetically engineer ensheathing cells to make them even more effective (L. Cao et al., 2004).
3. To use neurotrophic factors and/or adhesive molecules (see Chapter 7) to entice the axons of surviving neurons to grow across the damaged region of spinal cord (Hendriks et al., 2004) and reconnect to their targets (Harel and Strittmatter, 2006). In dogs, a nonspecific polymer, polyethylene glycol, seems to repair broken membranes when injected into spinal cord within a few days of injury. Dogs given this treatment were more than twice as likely to walk again (Laverty et al., 2004).
4. To transplant "regeneration-friendly" peripheral nerves to connect the brain and lower spinal cord by forming a "bridge" around the injured spinal cord (Bernstein-Goral and Bregman, 1993). This approach centers on the observation that axons in peripheral nerves, when cut by injury, will regrow and reconnect to their targets, yet cut axons in the CNS almost never accomplish this feat. No one really knows why peripheral and central axons differ in this regard, but it might be possible to exploit regeneration-friendly peripheral nerves to reconnect the spinal cord.

11.19 Leaders in the Campaign to Aid Victims of Spinal Paralysis Actor Christopher Reeve and his wife, Dana, were guests of honor at a meeting held in 1999 by the Society for Neuroscience to mark the achievements of the Decade of the Brain. Reeve received the Special Achievement Award for his efforts to raise public awareness of spinal cord injury and for promoting research funding with the Christopher Reeve Foundation (www.christopherreeve.org). Tragically, he died in 2004 from adverse reactions to antibiotic treatment, and his widow Dana died of cancer just 2 years later. (Courtesy of the Society for Neuroscience.)

Cerebral cortex pathology causes some motor impairments

The most common motor impairments that follow strokes or injury to the human cerebral cortex are paralysis (**plegia**) or weakness (**paresis**) of voluntary movements, usually on one side of the body (*hemiplegia* and *hemiparesis*). Usually the paralysis appears on the side of the body opposite the injured hemisphere. In addition, affected patients show some **spasticity**, especially increased rigidity in response to forced movement of the limbs.

Spasticity reflects the exaggeration of stretch reflexes that have been released from the inhibition they usually receive from the cortex. Abnormal reflexes occur, such as the flaring and extension of the toes elicited by stroking the sole of the foot (the Babinski reflex). In the months following cerebral cortical injury, the clinical picture changes. The initial paralysis slowly diminishes, and some voluntary movements of the limbs return, although fine motor control of fingers is seldom regained. In humans the symptoms are more severe than in many other mammals.

Damage to nonmotor zones of the cerebral cortex, such as some regions of parietal or frontal association cortex, produces more-complicated changes in motor control. One such condition is **apraxia** (from the Greek *a-*, "not," and *praxis*, "action"), the inability to carry out purposeful acts even though paralysis or weakness is not evident and language comprehension and motivation are intact. Apraxia is illustrated in the following example: When asked to smile, a patient is unable to do so, although he certainly at-

plegia Paralysis, the loss of the ability to move.

paresis Partial paralysis.

spasticity Markedly increased rigidity in response to forced movement of the limbs.

apraxia An impairment in the ability to begin and execute skilled voluntary movements, even though there is no muscle paralysis.

timing of events at several stations in the nervous system for this task (Thorpe and Fabre-Thorpe, 2001). The time shown at each station in **Figure 11.23** is a typical average latency from the start of the stimulus. Activity proceeds from the primary visual cortex through the ventral *what* pathway (recall that this is the visual pathway that was damaged in patient D.F., impairing her ability to recognize objects; see Chapter 10) to prefrontal cortex, then through premotor and primary motor cortex, down to the spinal motoneurons, and out to the finger muscles. It is fascinating to think that something like this sequence of neural events happens over and over in more-complicated behaviors, such as recognizing a long lost friend or composing an opera.

Summary

1. There are two broad categories of motor activity: movements and acts. Reflexes are simple movements; more-complex motor behaviors are acts. Complex acts indicate the existence of a motor plan.
2. Reflexes are patterns of relatively simple and stereotyped movements elicited by the stimulation of sensory receptors; their amplitude is proportional to the intensity of the stimulation.
3. Many reflexes are controlled by closed-loop, negative feedback circuits. Some behaviors are so rapid, however, that they are controlled by open-loop systems; that is, the pattern is preset and does not respond to feedback.
4. Motor control systems are organized into a hierarchy that consists of the skeletal system and associated muscles, the spinal cord, the brainstem, and various parts of the brain, including the primary and nonprimary motor cortices, the cerebellum, and the basal ganglia.
5. Muscles around a joint work in pairs. Antagonists work in opposition; synergists work together.
6. Smooth muscles, such as those in the stomach, are under involuntary control; striated muscles are under voluntary control.
7. Action potentials travel over motor nerve fibers (axons from motoneurons) and reach muscle fibers at the neuromuscular junction, releasing acetylcholine to trigger muscle contraction.
8. The final common pathway for impulses to skeletal muscles consists of motoneurons whose cell bodies in vertebrates are located in the ventral horn of the spinal cord and within the brainstem. The motoneurons receive impulses from a variety of sources, including sensory input from the dorsal spinal roots, other spinal cord neurons, and descending fibers from the brain.
9. Muscle spindles and Golgi tendon organs—sensory receptors in the muscles and tendons, respectively—transmit a wide range of information about muscle activities to the central nervous system. The sensitivity of the muscle spindle can be adjusted by efferent impulses that control the length of the spindle. This adjustment allows flexible control of posture and movement.
10. When a muscle is stretched, a reflex circuit often causes contraction, which works to restore the muscle to its original length; this response is called the stretch reflex. The stretch of the muscle is detected by muscle spindles.
11. The pyramidal (corticospinal) tract is especially well developed in primates and is involved mainly in controlling fine movements of the extremities. Its fibers originate mainly in the primary motor cortex (M1) and adjacent regions, and they run directly to spinal motoneurons or to interneurons in the spinal cord. Nonprimary motor cortex helps control the sequence of movements. Premotor cortex contains mirror neurons that are active when an individual is moving an object in a particular fashion, or when the individual sees someone else moving an object in that manner.
12. Although the centers of representation of body parts are separated in an orderly fashion in M1, the subregional organization is broadly distributed, and each M1 neuron influences many muscles. M1 is involved in learning motor responses and in cognitive processes such as encoding serial order.
13. Extrapyramidal brain regions that modulate movement include the basal ganglia (caudate nucleus, putamen, and globus pallidus), some major brainstem nuclei (substantia nigra, thalamic nuclei, and red nucleus), and the cerebellum.

Refer to the
LEARNING BIOLOGICAL PSYCHOLOGY WEBSITE
www.biopsychology.com
for study questions, animations, activities and other study aids.